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Lavonas EJ, Buchanan J.
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Cochrane Database of Systematic Reviews 2015, Issue 9. Art. No.: CD007951.
DOI: [10.1002/14651858.CD007951.pub2](https://doi.org/10.1002/14651858.CD007951.pub2).

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[Intervention Review]

Hemodialysis for lithium poisoning

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ABSTRACT

Background

Lithium salts, particularly lithium carbonate, are frequently used to treat bipolar disorder and mania. Lithium poisoning, which can occur as a result of reduced renal elimination, prescribing error, drug-drug interactions, or deliberate overdosage, produces neurologic injury that can be permanent. Hemodialysis is often recommended to treat lithium poisoning. Although hemodialysis clearly enhances the elimination of lithium, it is unclear whether this translates into improved patient outcomes. Evidence from observational studies, generally of low methodological quality, shows similar outcomes in patients managed with or without the use of hemodialysis.

Objectives

To determine whether hemodialysis, applied in addition to standard therapy, reduces the likelihood, severity, or duration of neurological sequelae following lithium poisoning.

Search methods

We ran the search on 15 May 2015. We searched the Cochrane Injuries Group's Specialised Register, Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*), MEDLINE (OvidSP), Embase Classic+Embase (OvidSP), CINAHL Plus, clinical trials registers and four other databases. We screened the reference lists of relevant studies, textbook chapters, and review articles, and performed a Google search to identify grey literature.

Selection criteria

In the context of this review, hemodialysis was defined as any extracorporeal technique to filter and extract toxicants from the serum, including all forms of hemodialysis, hemofiltration, and continuous renal replacement techniques, but not peritoneal dialysis. We included any clinical trials in which patients were randomly allocated to receive, or not receive, hemodialysis in addition to standard care for lithium poisoning.

Data collection and analysis

Two authors reviewed the abstracts of all identified articles. If either author identified an article as potentially meeting the inclusion criteria, both authors reviewed the full text of the article.

Main results

No randomized controlled trials of hemodialysis therapy for lithium poisoning were identified.

Authors' conclusions

Although the use of hemodialysis to enhance the elimination of lithium in patients with lithium poisoning appears logical, there is no evidence from randomized controlled trials to support nor refute the use of hemodialysis in the management of patients with lithium poisoning.

PLAIN LANGUAGE SUMMARY**Hemodialysis for lithium poisoning****Background**

Lithium salts, particularly lithium carbonate, are frequently used to treat bipolar disorder and mania. Lithium poisoning, whether due to reduced excretion by the kidneys or overdose, can cause permanent injury to the nervous system. Hemodialysis is a process in which a person's blood is filtered outside of their body, by a machine, and then returned to the person's body. Hemodialysis effectively removes lithium from the body, and has been used to treat lithium poisoning for at least 40 years. However, it is not known whether hemodialysis, performed in addition to standard therapy with intravenous fluids, reduces or eliminates damage to the nervous system.

Search date

The information in this review is up to date to 15 May 2015.

Study characteristics

This review found no randomized controlled trials assessing the use of hemodialysis to treat lithium poisoning.

Key results

Although the use of hemodialysis to remove lithium from patients with lithium poisoning is logical, no randomized clinical trials support or disprove a benefit from this therapy.

BACKGROUND

Lithium salts, particularly lithium carbonate, are frequently administered for the treatment of bipolar disorder and mania. Lithium is a metal, and therefore cannot be metabolised. It is eliminated almost exclusively (95%) through the kidney, with a small amount (5%) eliminated in sweat and saliva (Baldessarini 2001). Lithium clearance is dependent on the glomerular filtration rate (GFR). Steady-state lithium concentrations are highly dependent on hydration status; because lithium causes a nephrogenic diabetes insipidus, mild dehydration can lead to lithium accumulation and further dehydration. Lithium is also subject to a large number of pharmacokinetic interactions, most notably with hydrochlorothiazide, other diuretics, angiotensin converting enzyme (ACE) inhibitors, and non-steroidal antiinflammatory drugs (NSAIDs) (Juurlink 2007). Possibly for these reasons, unintentional lithium poisoning is more common in older people (Juurlink 2007). However, as with other psychiatric medications, lithium is frequently taken in deliberate overdose.

Lithium has a narrow therapeutic index. Serum lithium levels of 0.6 to 1.2 mmol/L are typically targeted for therapeutic effect (Amdisen 1977). Although there is no clear relationship between serum or cerebrospinal fluid (CSF) lithium concentrations and toxic effects (Hansen 1978), signs of lithium poisoning, including altered mental status, tremor, cerebellar dysfunction, and extrapyramidal signs, are common when serum lithium levels exceed 1.5 to 2.0 mmol/L (Gadallah 1988). As a result, lithium poisoning is a common medical condition. The 2013 report of the American Association of Poison Control Centers lists 2883 cases of lithium poisoning treated in healthcare facilities, including 1333 cases with moderate or major severity outcomes and five deaths (Mowry 2014). Unintentional ingestions and adverse reactions outnumbered intentional overdoses by nearly a 2:1 margin.

Lithium poisoning is generally classified as acute (associated with a deliberate overdose in a patient not concurrently taking lithium therapeutically), acute-on-chronic (associated with a deliberate overdose in a patient on lithium therapy), or chronic (related to gradual accumulation due to chronic overdosage, pharmacokinetic interactions, and/or impaired elimination) (Greller 2015). The severity of lithium poisoning is typically graded based on a standard scale (Hansen 1978).

Hemodialysis is a medical procedure in which blood is removed from a large vein, filtered to balance electrolytes, remove excess fluids, and remove endogenous and exogenous toxins, and returned to the body. Because of its low molecular weight (74 daltons), water solubility, relatively low volume of distribution (0.8 L/kg), and minimal protein binding, lithium is highly amenable to removal by hemodialysis. The renal clearance of lithium (15 to 20 ml/min) increases four- to ten-fold during hemodialysis, to 87 to 160 ml/min (Jacobsen 1987; Jaeger 1993; Eyer 2006). Because lithium is slow to partition between the serum/plasma and intracellular compartments, a rebound in serum lithium levels commonly follows hemodialysis sessions (Amdisen 1969; Von Hartitzsch 1972). This rebound does not affect the CSF; spinal fluid lithium concentrations continue to decline after hemodialysis (Amdisen 1969; Jaeger 1985).

Although the kinetics of lithium elimination are well understood, the question of whether enhancing the elimination of lithium through hemodialysis improves outcomes is more complex.

Concentrations of lithium measured in the serum (Hansen 1978; Gadallah 1988; Jaeger 1993; Eyer 2006), red blood cells (El Balkhi 2009), or CSF (Amdisen 1969; Jaeger 1985) do not correlate well with clinical severity. Rapid fluid shifts associated with hemodialysis have the potential to cause harm, and one retrospective study reported a temporal association between hemodialysis and neurologic deterioration (Swartz 1994).

Description of the condition

Whether due to acute, chronic, or acute-on-chronic poisoning, lithium poisoning can produce alteration in mental status, tremors, hyperreflexia/clonus, cerebellar dysfunction, extrapyramidal signs, cardiac conduction abnormalities, diabetes insipidus, seizures, and death. Death from lithium poisoning is uncommon; when it occurs, it is generally related to complications (e.g. aspiration pneumonitis) or co-morbidities. Cardiac conduction abnormalities and diabetes insipidus are both concentration-dependent phenomena that develop in a small minority of patients; these typically resolve after lithium levels decline. However, neurologic sequelae of lithium poisoning, including impaired cognition, cerebellar dysfunction, and parkinsonian findings, may be permanent. This condition is sometimes referred to as the syndrome of irreversible lithium-effectuated neurotoxicity (SILENT) (Adityanjee 2005). The incidence of this condition, and the proportion of patients who present with acute, chronic, or acute-on-chronic lithium poisoning who develop SILENT, are not known.

Description of the intervention

Standard therapy for lithium poisoning consists of discontinuation of lithium therapy, discontinuation of any medications that would impair the elimination of lithium, and intravenous hydration. In addition, many subject-matter experts recommend hemodialysis to enhance the elimination of lithium, though the specific clinical indications for hemodialysis vary (Hansen 1978; Amdisen 1988; Schneider 2000; Miller 2004; Decker 2015; Greller 2015). Subject-matter experts do not agree on specific indications for hemodialysis. Common recommended indications include alterations in mental status, renal insufficiency, or serum lithium levels exceeding an arbitrarily-defined threshold, typically ≥ 4.0 or 5.0 mEq/L for acute poisoning and ≥ 2.0 mEq/L for chronic poisoning (Amdisen 1988; McKnight 2012; Decker 2015; Greller 2015).

How the intervention might work

When a critical toxic concentration (perhaps 1.5 to 2.0 mEq/L) is exceeded, lithium toxicity appears to be both a dose- and time-dependent phenomenon. Hemodialysis rapidly removes lithium from the serum, creating a steep concentration gradient that reduces the levels of lithium in the central nervous system and other target tissues more quickly than the reduction achieved by hydration alone (Amdisen 1969; Von Hartitzsch 1972; Jaeger 1985). In theory, reducing the area under the lithium concentration-time curve by rapidly reducing serum and/or CSF lithium concentrations might reduce the severity of neuronal injury.

Why it is important to do this review

Hemodialysis is widely advocated as a means of reducing the risk of permanent neurological sequelae following lithium poisoning. According to standard reference sources (textbooks and review articles), this recommendation appears to be based on a

theoretical model of the problem, rather than on the results of human or animal experimentation or prospective clinical research (Amdisen 1988; Schneider 2000; Osborn 2001; Miller 2004; Thundiyil 2007; Hung 2014; Decker 2015; Greller 2015). A recent study showed substantial variation in recommended treatment when standardized lithium poisoning cases were presented to a large number of physicians in a single specialty (Roberts 2014).

Evidence from observational studies, generally of low methodologic quality, shows similar outcomes in patients managed with or without the use of hemodialysis. Most of these were retrospective: studies with prospective data collection were designed to study other aspects of lithium poisoning, such as pharmacokinetics, and therefore should be regarded as having a retrospective study design with regard to this clinical question. All are subject to confounding by indication (because sicker patients were more likely to receive hemodialysis in addition to standard therapy) and few clearly describe the method by which outcomes were assessed.

In the United States, the use of hemodialysis to treat lithium poisoning seems to be increasing over time (Holubek 2008). Hemodialysis is somewhat expensive, particularly when its application requires that a patient be transferred from one hospital to a second hospital with the capability to perform hemodialysis. The hemodialysis procedure is associated with a 1% risk of significant complications, including catheter-related complications and neurological injury induced by fluid and electrolyte shifts. A systematic review of 93 published case reports suggest that it may actually worsen neurological outcomes in lithium poisoning (Swartz 1994). This review investigates whether hemodialysis and related modalities of extracorporeal removal provide a safe and effective means of mitigating neurotoxic sequelae of lithium poisoning.

OBJECTIVES

To determine whether hemodialysis, applied in addition to standard therapy, reduces the rate, severity, or duration of neurological sequelae following lithium poisoning.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials investigating the effect of hemodialysis on outcomes in lithium poisoning in humans, regardless of language, date, or state of publication (abstract versus full report).

Types of participants

Patients (of any age) with the laboratory-confirmed diagnosis of acute, chronic, or acute-on-chronic lithium poisoning. Lithium poisoning may be defined by each study author, with no attempt to define, a priori, which inclusion criteria are appropriate for each study. Laboratory confirmation may consist of a measured serum lithium level greater than a threshold defined by the individual study author. We excluded studies recruiting patients who had been simultaneously exposed to multiple neurotoxic agents.

Types of interventions

Hemodialysis (including high flow intermittent hemodialysis and hemofiltration) or related methods of extracorporeal drug elimination (e.g. continuous arterio-venous hemofiltration, continuous veno-venous hemofiltration, continuous renal replacement therapy, etc.).

For the purposes of this review, hemodialysis is defined as standard intermittent dialysis, using either a standard or high-flux membrane, including slow continuous hemodialytic techniques (e.g. continuous arterio-venous hemofiltration, continuous veno-venous hemofiltration, continuous arterio-venous hemodialysis, continuous veno-venous hemodialysis, or slow continuous ultrafiltration).

We did not consider studies of peritoneal dialysis because this intervention is rarely studied or recommended for lithium removal.

We planned to compare results obtained with hemodialysis with results obtained with standard care. Standard care for lithium poisoning includes cessation of lithium administration, cessation of any medications that reduce lithium elimination (e.g. thiazide diuretics, angiotensin converting enzyme (ACE) inhibitors), intravenous hydration with isotonic crystalloid solution, and treatment of comorbid conditions.

Had studies of slow continuous hemodialytic techniques been found, these would have been the subject of a planned subgroup analysis.

Types of outcome measures

Primary outcomes

- Neurologic abnormalities, using any valid assessment criteria (for example, formal neuropsychological assessment, validated tests of various domains of neurological function (e.g. Trail Making A and B, etc., Bowie 2006), formal cognitive assessment (e.g. Folstein mini-mental status examination (Folstein 1975)), or structured physician assessment)

Secondary outcomes

- Mortality
- Incidence and severity of disability (ability to work or perform other activities of daily living)
- Length of hospital stay
- Complications of therapy

Search methods for identification of studies

In order to reduce publication and retrieval bias we did not restrict our search by language, date or publication status.

Electronic searches

The Cochrane Injuries Group Trials Search Co-ordinator and the authors searched the following:

1. Cochrane Injuries Group Specialised Register (15 May 2015);
2. Cochane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*, issue 4, 2015);

3. Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid OLDMEDLINE(R) (1946 to 15 May 2015);
4. EMBASE Classic + EMBASE (1947 to 15 May 2015);
5. CINAHL Plus (1937 to 15 May 2015);
6. ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED) (1970 to 15 May 2015);
7. ISI Web of Science: Conference Proceedings Citation Index-Science (CPCI-S) (1990 to 15 May 2015);
8. ZETOC: British Library's table of contents of journal articles and conference proceedings (<http://zetoc.mimas.ac.uk/>) (15 May 2015);
9. TOXNET (15 May 2015);
10. Current Awareness in Clinical Toxicology (<http://www.npis.org/cact.html>) (January 1999 to 4 June 2015);
11. ISRCTN (<http://www.isrctn.com/>) (4 June 2015);
12. Clinicaltrials.gov (www.clinicaltrials.gov) (4 June 2015).

Search strategies are reported in [Appendix 1](#).

We adapted the MEDLINE search strategy illustrated in Appendix 1 as necessary for each of the other databases. We used search filters, a modified version of the "Cochrane Highly Sensitive Search Strategies", for identifying randomized trials in MEDLINE and Embase ([Lefebvre 2011](#)).

Searching other resources

The authors searched the reference lists of all relevant studies, chapters on lithium poisoning and extracorporeal removal of toxins from several major English-language textbooks ([Schneider 2000](#); [Miller 2004](#); [Osborn 2001](#); [Thundiyil 2007](#); [Hung 2014](#); [Greller 2015](#)) and all review articles published since 2010 ([Bayliss 2010](#); [McKnight 2012](#); [Decker 2015](#)). In addition, the authors contacted experts in the field in order to identify ongoing and unpublished studies as

well as running general Internet searches, using terms selected from the search strategy, to identify grey literature.

Data collection and analysis

We performed a systematic review following the instructions given in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)).

Selection of studies

Two review authors independently scanned the titles and abstracts of all articles identified by the search strategy. If either or both authors identified the article as possibly meeting the inclusion criteria, the authors obtained the full text of the article from the University of Colorado Health Sciences Library. Both authors then reviewed the full text of each article to make a final determination whether the article met the inclusion criteria. Disagreement between review authors was resolved by consensus.

Had we identified any articles meeting the inclusion criteria, we would have analysed them according to the criteria described in [Appendix 2](#).

RESULTS

Description of studies

Results of the search

We found 504 articles through database searching and an additional 36 articles through the review of references ([Figure 1](#)). We reviewed the full text copy of 25 articles. None were clinical trials. We did not identify any ongoing or completed trials in the trials registries searched. Several textbook chapters and review articles affirmed that no clinical trials have been conducted, and the experts contacted could identify no clinical trials that might meet the inclusion criteria.

Figure 1. Study flow diagram

Included studies

We identified no studies meeting the inclusion criteria.

Excluded studies

The available literature contains single case reports and retrospective observational studies. Neither study design meets the inclusion criteria. The retrospective studies are described individually in the [Characteristics of excluded studies](#) section.

Risk of bias in included studies

We identified no studies meeting the inclusion criteria. If studies are identified in the future, they will be assessed according to the criteria in [Appendix 2](#).

Effects of interventions

We identified no studies meeting inclusion criteria.

DISCUSSION

Summary of main results

To date, no clinical trials have been published evaluating the use of hemodialysis for the treatment of lithium poisoning. We did not identify any unpublished or ongoing trials.

Overall completeness and applicability of evidence

No randomized controlled trials were identified, and there are no studies included in this review.

Potential biases in the review process

The search for studies was conducted by an independent information scientist, employed by the Cochrane Injuries Group, and independent review of studies by the co-author (JB) would likely have identified any relevant studies.

Agreements and disagreements with other studies or reviews

In 2015, the Extracorporeal Treatments in Poisoning (EXTRIP) workgroup (www.extrip-workgroup.org) published a systematic review and treatment recommendations for the use of dialysis in lithium poisoning ([Decker 2015](#)). A total of 166 articles were found, mostly case reports, yielding a very low quality of evidence for all recommendations. The workgroup concluded that lithium is dialyzable, and recommended dialysis in cases of severe lithium poisoning, defined by various combinations of elevated serum lithium concentrations, renal function, and alteration of mental status. The reason for the different conclusions between the EXTRIP review and the current review is methodological; in addition to clinical trial evidence, the EXTRIP workgroup's methodology also

permits consideration of observational studies, case series, case reports, animal studies, and in vitro studies, and explicitly considers pharmacokinetic data when making treatment decisions ([Lavergne 2012](#)). EXTRIP authors note that their expert opinion was based on pharmacokinetic considerations and very low quality clinical data. In contrast, this review includes only randomized controlled trials.

The authors of textbook chapters, review articles, and other published reports generally recommend the use of hemodialysis for select patients with lithium poisoning. Clinical indications vary, but typical recommendations include the use of hemodialysis for patients who have altered mental status, chronic lithium poisoning, and/or renal impairment. Most but not all authors acknowledge the lack of clinical trials data to support these treatment recommendations.

AUTHORS' CONCLUSIONS

Implications for practice

Although the use of hemodialysis to enhance the elimination of lithium in patients with lithium poisoning is logical, there is no research from randomized controlled trials on its benefits and harms in patients with lithium poisoning. Most patients with lithium poisoning recover fully, but the available data do not provide a reliable way to predict which patients will have a good or poor outcome. Until higher-quality evidence can be developed, the decision to use hemodialysis in addition to standard therapy with intravenous fluids will continue to be based on clinical judgment. Hemodialysis treatment should ideally be given as part of a randomized controlled trial.

Implications for research

There are no randomized controlled trials on which to assess the clinical effects of hemodialysis for lithium poisoning, nor is there a strong preponderance from observational studies suggesting that a benefit is present. A randomized controlled trial of hemodialysis for lithium poisoning is ethical and reasonable. If a randomized trial is not feasible, useful information may be gained from a prospective observational study with standardized outcome assessment, utilizing propensity adjustment methods to reduce the bias imparted by confounding by indication.

ACKNOWLEDGEMENTS

The authors acknowledge and thank Ms. Emma Sydenham for her gracious and patient support through the editorial process, and Ms. Karen Blackhall and Ms. Deirdre Beecher of the Cochrane Injuries Group for developing the search strategy.

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CHARACTERISTICS OF STUDIES

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Amdisen 1969	Excluded due to design (single case report) This single case report shows serial measurements of lithium concentrations in the serum and cerebrospinal fluid during and after hemodialysis. It provides unique pharmacokinetic data but cannot be used to evaluate the effect of dialysis on clinical outcomes.
Bailey 2000a	Excluded due to design (retrospective observational study). Focuses on patient outcomes with and without dialysis. Participants were 205 patients with lithium poisoning (174 chronic, 31 acute or acute-on-chronic) reported to a poison control center. Nine patients (4.4%) received hemodialysis. Among patients who received dialysis, 1/9 (11%) had neurologic sequelae and 2/9 (22%) died. Among patients who did not receive dialysis, 1/196 (0.5%) died and 195/196 (99%) recovered without neurologic sequelae. In addition, one patient with chronic lithium poisoning who had resolution of neurologic symptoms but persistent renal insufficiency; this patient's treatment was not described.
Bailey 2000b	Excluded due to design (retrospective observational study) This study reports the same population as in Bailey 2000a , with a different emphasis. It compares outcomes in patients for whom the regional Poison Center recommended dialysis and those for whom the Center recommended management without dialysis. The conclusion is that dialysis recommendations were often disregarded with no apparent impact on outcomes.
Bretaudeau Deguigne 2013	Excluded due to design (retrospective observational study) Participants were 103 patients with lithium poisoning reported to a poison control center. 11/103 (11%) received dialysis. 2/103 (2%) patients died, one from complications of hemodialysis (hemorrhagic shock from a catheterization accident) and the other from respiratory complications of severe encephalopathy and myoclonus. Long-term outcomes in the 101 survivors were not described.
Decker 2015	Excluded due to design (systematic review; no eligible trials were included)
Dyson 1987	Excluded due to design (retrospective observational study) Participants were 68 patients with lithium poisoning (25 chronic, 43 acute). One patient received dialysis because of acute renal failure; the rest were managed with oral or intravenous fluids only. 67/68 patients (99%) recovered without sequelae. The patient who received dialysis had persistent parkinsonism lasting 3 months.
El Balkhi 2009	Excluded due to design (review article)

Study	Reason for exclusion
Eyer 2006	<p>Excluded due to design (retrospective observational study)</p> <p>Participants were 22 patients with lithium poisoning, of whom 9/22 (41%) received hemodialysis. 1/22 patients (5%) died from pre-existing pulmonary fibrosis; clinical outcomes in the 21 survivors were not described.</p>
Gadallah 1988	<p>Excluded due to design (retrospective observational study)</p> <p>Participants were 55 patients with lithium poisoning (13 chronic, 42 acute-on-chronic).</p> <p>A retrospective observational study evaluated outcomes in 55 patients with lithium poisoning. Of these, 13 had chronic lithium poisoning and 42 had acute or acute-on-chronic overdosage. All patients received intravenous saline hydration, and 6 patients (11%) also received hemodialysis. All patients (55/55, 100%) recovered without neurological sequelae.</p>
Hansen 1978	<p>Excluded due to design (retrospective observational study)</p> <p>Participants were 23 patients with lithium poisoning (21 chronic, 2 acute). Sixteen patients (70%) received hemodialysis, while the other seven patients received forced diuresis with hypertonic saline infusions (3000 to 6000 mL of 300 to 600 millimolar sodium chloride solution over 24 hours), a treatment that would now be considered dangerous. Thirteen of 14 patients who had grade III neurotoxicity ("stupor", "coma", and/or "latent convulsive movements") received hemodialysis, while 3 of 9 patients with lesser severity neurotoxicity were dialyzed. Two patients died, one each in the dialysis and no-dialysis groups, and neurologic outcome was not reported in one survivor. Of the remaining patients, 13/15 (87%) patients treated with dialysis and 4/4 (100%) patients managed without dialysis recovered without neurologic sequelae.</p> <p>The authors also performed a systematic review of 100 case reports of lithium toxicity published between 1949 and 1973. No critical analysis of the effect of hemodialysis can be extracted from this review.</p>
Holubek 2008	<p>Excluded due to design (review article)</p>
Jacobsen 1987	<p>Excluded due to design (retrospective observational study)</p> <p>Participants were 4 patients with acute lithium poisoning. All received hemodialysis. No patient (0/4, 0%) had neurologic sequelae; one patient had diabetes insipidus lasting 6 weeks.</p>
Jaeger 1985	<p>Excluded due to design (case report with pharmacokinetic analysis)</p> <p>This single case report shows serial measurements of lithium concentrations in the serum, cerebrospinal fluid, urine, and dialysate before, during, and after three sessions of hemodialysis. It provides unique pharmacokinetic data but cannot be used to evaluate the effect of dialysis on clinical outcomes.</p>
Jaeger 1986	<p>Excluded due to design (retrospective observational study)</p> <p>Participants were three patients with lithium poisoning, two of whom were treated with hemodialysis. Pharmacokinetic data, but not clinical outcomes, are reported.</p>
Jaeger 1993	<p>Excluded due to design (retrospective observational study)</p> <p>Participants were 14 patients with lithium poisoning (5 chronic, 7 acute-on-chronic, 2 acute). 3/14 (21%) were treated with dialysis. All patients recovered without sequelae. Detailed data were presented on lithium kinetics.</p>
Leblanc 1996	<p>Excluded due to design (retrospective observational study)</p> <p>Participants were 7 patients with lithium poisoning, all of whom were treated with continuous arteriovenous or venovenous hemodiafiltration. 4/7 patients (57%) recovered fully. 2/7 patients (29%)</p>

Study	Reason for exclusion
	survived with persistent neurologic sequelae from lithium poisoning, and one additional patient developed a non-hemorrhagic stroke approximately two days after completing the hemodiafiltration procedure.
Lee 2011	Excluded due to design (retrospective observational study) Participants were 21 patients with lithium poisoning reported to a poison control center. 3/21 (14%) patients received hemodialysis. All patients (21/21, 100%) recovered without chronic sequelae.
Meltzer 2002	Excluded due to design (retrospective observational study) Participants were 8 patients with lithium poisoning treated at a single institution over a 10-year period. One case was presented in detail: a 55 year old woman with severe illness who was managed without dialysis and developed neurologic sequelae. The treatment and outcomes in the other seven patients were not described.
Montagnon 2002	Excluded due to design (retrospective observational study) Participants were 81 patients with lithium poisoning treated in a single intensive care unit. Hemodialysis was used in "3-6 percent" of cases. 3/81 (4%) patients died, 1/81 (1%) had persistent neurologic findings, 2/81 (2%) had diabetes insipidus, and 75/81 (93%) recovered fully.
Offerman 2010	Excluded due to design (retrospective observational study) Participants were 502 patients with lithium poisoning who were admitted to acute-care hospitals and whose cases were reported to a state-wide poison center system. 69/502 (14%) patients received hemodialysis. 4/502 patients (1%) died. Neurologic outcomes were not reported in the survivors. The authors observed that, although 14/69 (20%) of patients had 'rebound' increases in serum lithium concentration after conclusion of hemodialysis, in no case was this accompanied by worsening signs or symptoms of poisoning.
Schou 1984	Excluded due to design (unstructured literature review) Participants were 40 patients with lithium poisoning. Treatment provided was not reported.
Swartz 1994	Excluded due to design (retrospective observational study + systematic review) The authors present three cases from their institution involving patients with lithium poisoning. It is not clear whether these were consecutive patients or selected from a larger population. One patient was treated with discontinuation of lithium only, one with discontinuation plus peritoneal dialysis, and one with discontinuation plus hemodialysis. All three patients developed transient neurologic deterioration following treatment. One patient recovered fully and two developed lasting neurologic sequelae. The authors then performed a systematic review, locating 93 published case reports. As was common for the time, systematic review methods were not completely described. Ninety three cases of lithium poisoning were reported. Twenty eight patients did not develop delirium at any time during their hospital course, and 15 patients had delirium on admission. The literature review focused on the remaining 50 patients who developed delirium at some point during hospitalization. The authors noted a temporal association between initiation of hemodialysis and neurologic deterioration, and concluded that sudden discontinuation of lithium and dialysis may be harmful.
Von Hartitzsch 1972	Excluded due to design (retrospective observational study) Participants were 3 patients with lithium poisoning, treated with hemodialysis. 2/3 (67%) had neurologic sequelae and 1/3 (33%) recovered fully.
Waring 2007a	Excluded due to design (case report)

Study	Reason for exclusion
Waring 2007b	Excluded due to design (retrospective observational study) Participants were 172 patients with lithium poisoning (26 chronic, 39 acute-on-chronic, 88 acute) reported to a poison control center. Patients with chronic toxicity were noted to have more severe signs and symptoms of poisoning. No data about treatment or outcomes are provided.

APPENDICES

Appendix 1. Search strategies

Cochrane Injuries Group Specialised Register

#1 (toxicity) AND (INREGISTER)

#2 #1 OR #2

#3 ((renal or hemofiltration or hemodiafiltration or dialysis or dialyses)) AND (INREGISTER)

#4 #3 AND #4

CENTRAL (The Cochrane Library)

#1MeSH descriptor: [Lithium Carbonate] explode all trees and with qualifiers: [Poisoning - PO, Toxicity - TO]

#2MeSH descriptor: [Lithium Compounds] explode all trees and with qualifiers: [Poisoning - PO, Toxicity - TO]

#3MeSH descriptor: [Poisoning] explode all trees

#4MeSH descriptor: [Lithium] explode all trees

#5lithium near/5 poison*:ti,ab,kw (Word variations have been searched)

#6#3 and #4

#7#1 or #2 or #5 or #6

#8MeSH descriptor: [Renal Dialysis] explode all trees

#9MeSH descriptor: [Hemofiltration] explode all trees

#10MeSH descriptor: [Hemodiafiltration] explode all trees

#11H*modifiltration or h*modiafiltration or biofiltration*:ti,ab,kw (Word variations have been searched)

#12((Renal or extracorporeal) near/3 (dialysis or dialyses)):ti,ab,kw (Word variations have been searched)

#13h*modialysis or h*modialyses:ti,ab,kw (Word variations have been searched)

#14#12 or #13

#15(dialysis or dialyses):ti,ab,kw (Word variations have been searched)

#16#8 or #9 or #10 or #11 or #14 or #15

#17#7 and #16

Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid OLDMEDLINE(R)

1. exp Lithium/po, to [Poisoning, Toxicity]

2. exp Lithium Carbonate/po, to [Poisoning, Toxicity]

3. exp Lithium Chloride/po, to [Poisoning, Toxicity]

4. exp Lithium Compounds/po, to [Poisoning, Toxicity]

5. exp Poisoning/

6. exp Lithium/

7. 5 and 6

8. (lithium adj5 poison*).ab,ti.

9. 1 or 2 or 3 or 4 or 7 or 8

10. exp Renal Dialysis/

11. exp Hemofiltration/

12. exp Hemodiafiltration/

13. (H?emofiltration or h?emodiafiltration or biofiltration*).ab,ti.

14. (((Renal or extracorporeal) adj3 (dialysis or dialyses)) or h?emodialysis or h?emodialyses).ab,ti.

15. (dialysis or dialyses).ab,ti.

16. 10 or 11 or 12 or 13 or 14 or 15

17. 9 and 16

18. randomi?ed.ab,ti.

19. randomized controlled trial.pt.

20. controlled clinical trial.pt.

Hemodialysis for lithium poisoning (Review)

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21. placebo.ab.
22. clinical trials as topic.sh.
23. randomly.ab.
24. trial.ti.
25. Comparative Study/
26. 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
27. (animals not (humans and animals)).sh.
28. 26 not 27
29. 17 and 28

Embase Classic + Embase (OvidSP)

- 1.exp Lithium/
- 2.exp Lithium Carbonate/
- 3.exp Lithium Chloride/
- 4.exp Lithium Derivative/
- 5.1 or 2 or 3 or 4
- 6.exp Intoxication/
- 7.5 and 6
- 8.(lithium adj5 poison*).ab,ti.
- 9.7 or 8
- 10.exp Renal Replacement Therapy/
- 11.exp Hemofiltration/ or exp Continuous Hemofiltration/
- 12.exp Hemodiafiltration/ or exp Continuous Hemodiafiltration/
- 13.(H?emofiltration or h?emodiafiltration or biofiltration*).ab,ti.
- 14.(((Renal or extracorporeal) adj3 (dialysis or dialyses)) or h?emodialysis or h?emodialyses).ab,ti.
- 15.(dialysis or dialyses).ab,ti.
- 16.10 or 11 or 12 or 13 or 14 or 15
- 17.9 and 16
- 18.exp Randomized Controlled Trial/
- 19.exp controlled clinical trial/
- 20.randomi?ed.ab,ti.
- 21.placebo.ab.
- 22.*Clinical Trial/
- 23.randomly.ab.
- 24.trial.ti.
- 25.18 or 19 or 20 or 21 or 22 or 23 or 24
- 26.exp animal/ not (exp human/ and exp animal/)
- 27.25 not 26
- 28.17 and 27

CINAHL Plus

- S23S11 AND S22
S22S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21
S21MH quantitative studies
S20TX random* N3 allocat*
S19(MH "Random Assignment")
S18TX placebo*
S17(MH "Placebos")
S16TX randomi?ed N3 control* N3 trial*
S15TI ((singl* N3 blind*) or (doubl* N3 blind*) or (trebl* N3 blind*) or (tripl* N3 blind*)) or T1 ((singl* N3 mask*) or (doubl* N3 mask*) or (trebl* N3 mask*) or (tripl* N3 mask*)) or AB ((singl* N3 blind*) or (doubl* N3 blind*) or (trebl* N3 blind*)) or AB ((singl* N3 mask*) or (doubl* N3 mask*) or (trebl* N3 mask*) or (tripl* N3 mask*))
S14TX clinical N3 trial*
S13PT clinical trial*
S12(MH "Clinical Trials")
S11S4 AND S10
S10S5 OR S6 OR S9
S9S7 OR S8
S8TX h#mofiltration or h#modiafiltraion or biofiltration*
S7TX ((renal or extracorporeal) N3 (dialysis or dialyses)) OR h#modialysis or h#modialyses
S6TX dialysis or dialyses
S5(MH "Hemofiltration+") OR (MH "Hemodiafiltration")

Hemodialysis for lithium poisoning (Review)

S4S1 OR S2 OR S3

S3TX (lithium N5 poison*) OR intoxic*

S2(MH "Poisoning+") AND (MH "Lithium")

S1(MH "Lithium Carbonate/PO") OR (MH "Lithium Compounds+/PO") OR (MH "Lithium/PO")

Zetoc: British Library's table of contents of journal articles and conference proceedings

General: (Poison* and Lithium)

ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED) & Conference Proceedings Citation Index-Science (CPCI-S)

#1. TS=(lithium same poison*)

#2. TS=(hemofiltration or hemodiafiltration or biofiltration* or Hemofiltration or hemodiafiltration) OR TS=((Renal or extracorporeal) same (dialysis or dialyses)) OR TS=(hemodialysis or hemodialyses or hemodialysis or hemodialyses)

#3. #1 and #2

ISRCTN

Search: dialysis AND lithium"

Clinicaltrials.gov

dialysis AND lithium AND INFLECT EXACT "Interventional" [STUDY-TYPES]

Appendix 2. Methods to be used in future versions of this review

Should future searches discover clinical trials meeting inclusion criteria, the plan for analysis is as follows:

Two authors will independently review each article that meets the inclusion criteria, and extract data from the article onto a standard data extraction form. We will then compare these data forms. In the event of disagreement between the authors, we will seek the opinion of a third physician. In ambiguous cases and where there are insufficient data, we will attempt to contact the authors of the articles for further clarification and additional information. We will then grade studies for risk of bias, using the instructions given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Data extraction and management

Two authors will extract data on the following items onto a standard form.

- General information (title, authors, source, year of publication, years conducted, language, etc.)
- Trial characteristics: design, diagnostic ascertainment, standard care provided, randomization and allocation concealment, intervention provided, drop-out and loss-to-follow-up rates, methods of outcome assessment
- Patients: inclusion and exclusion criteria, sample size, baseline characteristics (age, acute/chronic/acute-on-chronic poisoning, clinical severity on enrolment, hydration status, etc.)
- Interventions: type, intensity, and duration of hemodialysis or related extracorporeal elimination modality employed
- Outcomes:
 - * incidence of neurological sequelae
 - * severity of neurological sequelae
 - * duration of neurological sequelae
 - * mortality (all causes)
 - * time to return to work and/or independent living
 - * ability to perform Activities of Daily Living (ADLs)
 - * complications of therapy

Assessment of risk of bias in included studies

We will assess included studies for risk of bias in the following areas:

- Sequence generation of the randomization process
 - * Low risk: using random-number tables, computer random-number generation, coin tossing, or other valid method
 - * Unclear risk: not described, or other method of allocation that may not be random
 - * High risk: sequence generation described, but is not one of the methods above

- Adequacy of allocation concealment
 - * Low risk: allocation concealment is described, and would not allow either investigators or subjects to know or influence treatment group assignment at the time of study entry. Acceptable methods include central randomization or serially-numbered, opaque, sealed envelopes.
 - * Unclear risk: trial either did not describe the method of allocation concealment, or reported an approach that was not clearly adequate
 - * High risk: the method of allocation is not concealed (e.g. alternating patients, odd-even day) or one in which the investigators or subjects could be aware of allocation prior to study commencement
- Blinding of outcome assessors
 - * Low risk: blinding of outcome assessors was clearly maintained
 - * Unclear risk: blinding of outcome assessors was stated, but not clearly maintained
 - * High risk: outcome assessors were not blinded to treatment group assignment, or the blinding was incomplete
 - * Because placement of a large central venous catheter for the sole purpose of providing a sham for hemodialysis is unethical, we do not anticipate that any study subjects or treating physicians will be blinded to their treatment assignment.
- Intention-to-treat (ITT) analysis
 - * Low risk: specifically reported by the authors that ITT analysis was undertaken, or report that makes it unmistakable that ITT was undertaken, for the primary analysis
 - * Unclear risk: ITT analysis was mentioned, but it is uncertain from the report whether this was fully carried out
 - * High risk: lack of ITT was confirmed on study assessment
- Completeness of outcome data
- Selectiveness of outcome reporting
- Other sources of bias

Based on the above elements, we will classify each study as having a 'low', 'unclear' or 'high' risk of bias.

Measures of treatment effect

We will assess included studies for the validity of their measures of treatment effect and outcome, to include the following information.

- Objectivity and validity
 - * Good: study uses a previously validated, generally accepted, and standardised method of assessing outcomes, such as
 - ☐ a validated neuropsychological test instrument (for example, the Mini-Mental Status Examination, trail-making tests, etc.)
 - ☐ a validated scoring system for ADLs
 - ☐ formal neuropsychiatric assessments conducted by a trained evaluator, such as a PhD psychologist
 - ☐ explicitly described neurological examinations conducted by physicians
 - * Fair: study uses a standardized instrument that has not been previously validated to assess neurological and/or functional outcome
 - * Poor: study uses patient self-report, report of relatives, unstructured physician report, or other method of assessment that is not standardized
- Appropriately timed
 - * Excellent: all participants are assessed at one or more pre-specified time points, at least six weeks after the acute phase of illness
 - * Good: all participants are assessed at one or more pre-specified time points after discharge from the acute-care hospital
 - * Fair: all participants are assessed at some time point after discharge from the acute-care hospital
 - * Poor: the timing of follow-up assessments are either too soon to reliably reflect long-term outcomes, occur only in response to symptoms, or are non-uniform in another way that decreases reliability.

Dealing with missing data

We will assess missing data and attrition rates for each of the included studies, and report the number of participants who are included in the final analysis as a proportion of all participants in the study. We will explicitly report differences in drop-out and loss-to-follow-up rates between different treatment arms. We will provide reasons given for missing data in the narrative summary, and ascertain the extent to which the results may be altered by missing data. We will also assess the extent to which studies have conformed to an ITT analysis.

Assessment of heterogeneity

We will use the Chi² test to assess for heterogeneity between trials, and the I² statistic to assess the extent of inconsistency.

Assessment of reporting biases

We will prepare funnel plots to investigate any relationship between effect size and study precision. Such a relationship could be due to publication or related biases, or due to systematic differences in study design, including outcomes assessment, between small and large

studies. If a relationship is identified, we will examine the clinical diversity of studies as a possible explanation for study heterogeneity and described in the text.

Data synthesis

We will analyse the data using Review Manager software ([RevMan 2014](#)). We will express results for dichotomous outcomes as risk ratio (RR) with 95% confidence intervals (CI) and continuous outcomes as mean differences (MD) or standardized mean differences (SMD). We will use a fixed-effect model for calculating summary estimates and their 95% confidence intervals (CI), unless there is significant heterogeneity, in which case we will calculate results using a random-effects model. We will present data in a 'Summary of findings' table.

Subgroup analysis and investigation of heterogeneity

Where possible, we will perform subgroup analysis based on the following factors, which are thought to affect the long-term outcome after lithium poisoning.

1. Poisoning type (acute, chronic, or acute-on-chronic)
 - a. if necessary, the acute-on-chronic group may be combined with the acute group
2. Mental status prior to treatment (normal or altered)
3. Type of hemodialysis performed (high-flow intermittent hemodialysis versus slow continuous methods)
4. Dose and duration of hemodialysis (total duration of extracorporeal removal, target clinical endpoints used, etc.)

Sensitivity analysis

To assess the robustness of conclusions, we will perform sensitivity analysis according to the objectivity and validity of outcomes assessment.

CONTRIBUTIONS OF AUTHORS

Drs. Lavonas and Buchanan drafted the protocol, completed the review, and are responsible for the content.

DECLARATIONS OF INTEREST

EL: Dr. Lavonas reports contractual relationships between pharmaceutical and medical device companies and his employer. All relationships benefitted his employer, not him personally. None of the work involved was related to the topic of this review, and none of the companies involved are known to have any current or planned products related to the topic of this review. Dr. Lavonas reports no competing interests of any kind related to the topic of this review.

JB: None known.

SOURCES OF SUPPORT

Internal sources

- Denver Health and Hospital Authority, USA.
Salary (both authors)

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

All steps described in the protocol were conducted in the review, with the following exceptions.

- The authors were unable to search Toxbase because the site is password protected. The authors subsequently learned that this resource does not include clinical trial data and therefore is not relevant to this systematic review.
- The following monthly files from Current Awareness in Clinical Toxicology could not be downloaded:
 - * 2011: May
 - * 1999: October

- The following monthly files from Current Awareness in Clinical Toxicology were searched using the CACT index, rather than a formal electronic search:
 - * 2002: January - July
 - * 2001: January - December
 - * 2000: January, March - July
 - * 1999: January - July, September, November - December
- The planned analyses of the risk of bias and results of included studies could not be completed because no studies meeting the inclusion criteria were identified.

The stated purpose of this review was to study hemodialysis in lithium poisoning. During the review, the authors identified studies involving continuous arteriovenous and venovenous hemodiafiltration and hemodialysis. These were considered eligible for inclusion, but no clinical trials meeting the other inclusion criteria were found. The authors also identified studies involving peritoneal dialysis and the use of 'intestinal dialysis' using ion binding resins (i.e. kaexylate); these studies were not considered eligible for inclusion in this review.

The title was changed from 'haemodialysis' to 'hemodialysis' to harmonise the title with the American spelling in the main body of the text.

NOTES

In future updates of this review, mortality and neurologic abnormalities will be primary outcomes.

INDEX TERMS

Medical Subject Headings (MeSH)

*Renal Dialysis; Lithium Carbonate [poisoning]; Lithium Compounds [*poisoning]; Poisoning [therapy]

MeSH check words

Humans