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ORIGINAL ARTICLE

Concurrent lithium and haemodialysis treatment: Clinical recommendations based on the literature and a multicentre survey

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Abstract

Introduction: Lithium has an irreplaceable role in the treatment of severe mood disorders, but declining renal function associated with its use leads to clinical dilemmas. Although not often applied, and requiring close monitoring and multidisciplinary actions, concurrent lithium and haemodialysis treatment (CLHT) is a feasible option. To our knowledge, however, there are no detailed consensus- or evidence-based treatment guidelines or directives on its delivery.

Methods: To fill this gap, we reviewed the literature and surveyed psychiatrists and nephrologists with experience in CLHT using a self-designed questionnaire. Our goal was to form an integrated picture of the current knowledge and clinical practices of CLHT and formulate practical recommendations for colleagues being confronted with patients with renal dysfunction requiring lithium to help manage their mood disorder.

Results: We identified 14 case reports and case series describing CLHT and one systematic review concluding CLHT to be effective. Ten nephrologists and six psychiatrists practising in the Netherlands completed our questionnaire, providing details on collaboration, lithium dosing regimens, serum level evaluations and additional amenities and services they deemed necessary during CLHT delivery.

Discussion: We found that CLHT appears to be safe and effective and argue that delivery is a shared responsibility and needs continuous multidisciplinary finetuning. To facilitate delivery, we provide a flowchart for the initiation or reinstatement of lithium therapy in haemodialysis patients and a practical guide for CLHT, including an easy-to-use rule of thumb for calculating the lithium target dose.

KEYWORDS
bipolar disorder, end-stage kidney disease, haemodialysis, lithium, mood disorder, renal replacement

1 | INTRODUCTION

Lithium is a major cornerstone in the treatment of severe mood disorders, most prominently bipolar disorder. In the treatment of this latter disorder, it is the most effective and most widely prescribed mood stabilising drug and is still regarded as the gold standard for maintenance treatment.[1] In a large network meta-analysis, lithium was highlighted as the most effective treatment for the prevention of both manic and depressive episodes,[2] while it has consistently been shown to independently reduce the risk of suicide.[3]

Unfortunately, lithium is a relatively complex drug both for patients and their psychiatrists. It has a narrow therapeutic window and requires close laboratory monitoring to obtain and maintain adequate therapeutic blood levels and avoid intoxications, while patients must be well instructed on its proper and safe use, including precepts about fluid intake and co-medication.

1.1 | Nephrotoxicity

Long-term use of lithium can lead to chronic tubulointerstitial nephropathy, which is associated with a gradual loss of kidney function that may progress to end-stage kidney disease (ESKD).[4] However, data concerning the prevalence and severity of lithium-induced kidney disease are heterogeneous.[4] Nielsen et al.[5] concluded that renal decline attributable to lithium appears to be less in more recent studies than previously described, possibly due to improved monitoring and lower target lithium levels. Furthermore, associations between chronic kidney disease (CKD) and lithium use might at least in part be attributable to bias.[6] However, in a recent cross-sectional cohort study lithium was found to account for additional renal loss, independent of the diagnosis.[7] Also recently, Golic et al. showed that in their three cohorts the risk of severe renal loss appears to be consistent over time since the 1980's.[8] Overall, only a very small minority of all lithium users develop ESKD.[5] Nevertheless, up to 25% of lithium users may develop clinically significant renal impairment.[4]

1.2 | Clinical dilemmas

Declining renal function can confront health professionals and patients taking lithium with difficult therapeutic considerations and clinical dilemmas requiring an integrated psychiatric and nephrological approach.[9] Studies on discontinuing lithium in cases with CKD show mixed results and the question of whether and when lithium should be discontinued is subject to an ongoing debate.[10,11] Patients and their caregivers may feel as being given the choice between two evils as either choice can have both psychiatric and nephrological risks.

Discontinuation of lithium treatment for medical reasons is associated with an increased risk of relapse[12] and may also increase the risk of suicide,[13,14] while the already impaired renal function is often irreversible or even progressive regardless of whether lithium is discontinued or not, particularly when the estimated glomerular filtration rate (eGFR) has dropped beneath 30–40 mL/min/173 m^2.[10,13,15–17]

1.3 | Concurrent treatment with lithium and haemodialysis

If renal deterioration is severe or has progressed to ESKD, renal replacement therapy is indicated. In this scenario, it is important to know that, although counterintuitive at first glance, concurrent treatment with lithium and haemodialysis (CLHT) is a feasible option.[18]

Because CLHT is rarely applied or reported on, it is difficult for clinicians to gain experience in tailored treatment regimens for individual patients. Intermittent haemodialysis leads to entirely different pharmacokinetics and requires different lithium dosing and monitoring. To our knowledge, there are no detailed consensus- or evidence-based treatment guidelines or directives on this topic. We hence reviewed the available literature on CLHT and also surveyed fellow psychiatrists and nephrologists who have experience with the combination treatment to obtain an integral representation of our current knowledge and clinical practices of CLHT with the goal to formulate practical recommendations for colleagues being faced with patients requiring dialysis who cannot go without lithium.

2 | EXPERIMENTAL PROCEDURES

The study was approved by the ethical committee of Reinier van Arkel Mental Health Institute.

2.1 | Review of the literature

We first conducted a review of the literature: on October 27, 2022, the PubMed database was searched using the terms "Lithium AND (dialysis OR h(a)emodialysis OR renal replacement)", without a specific time frame. Articles were considered suitable when they were either reviews, clinical trials, case reports or case series and described oral lithium treatment in haemodialysis-dependent patients. Papers on the treatment of lithium intoxication using haemodialysis were excluded.[19] References of included articles were screened for additional articles, which yielded one additional article eligible for review (see Figure 1). Of the articles selected after screening of the abstract two were excluded. In the first, lithium was not administered orally but added to the dialysate.[20] The second case report was excluded as it described a case of peritoneal dialysis.[21]

2.2 | Survey of current CLHT practices in the Netherlands

To obtain an overview of current practices among Dutch nephrologists and psychiatrists with respect to lithium use and renal dialysis we designed a questionnaire based on our own clinical experience, previous research and the theoretical appreciation of various aspects of CLHT. The survey consisted of both closed and open questions focusing on the following topics: collaboration between medical specialists, choices and considerations regarding lithium dosing regimens, serum level evaluations and amenities needed during CLHT.

Different approaches were used to find medical specialists that met the single inclusion criterion of having practical experience with

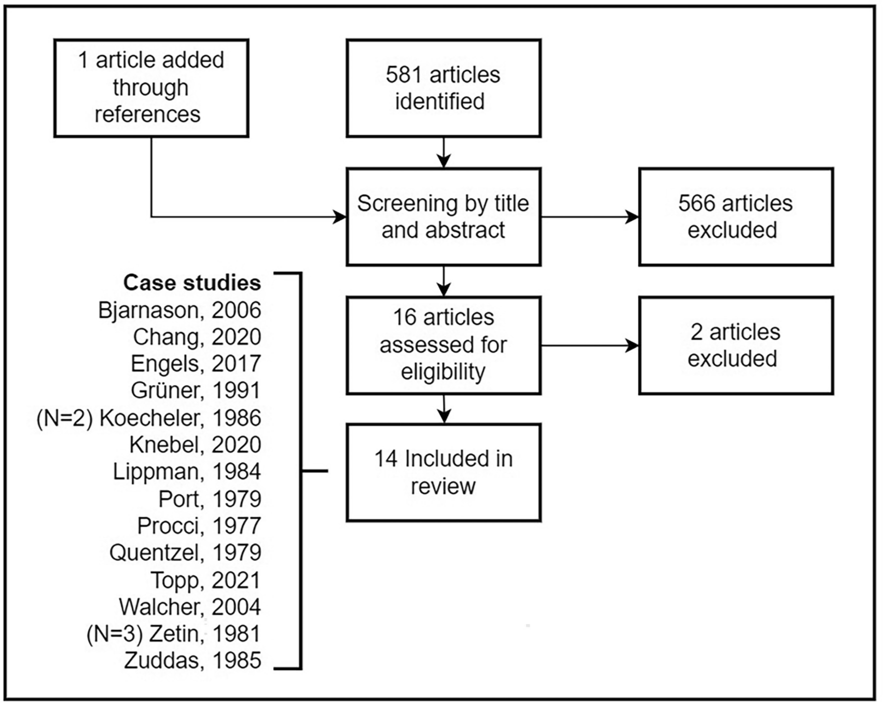

FIGURE 1 Flowchart of the article selection process.

CLHT. The questionnaire was distributed via the online newsletter of the Dutch Foundation for Bipolar Disorders (KenBIS) and our personal networks. Also, we contacted 98 dialysis centres in the Netherlands by telephone to inquire whether they had experience with treating patients that were concurrently using lithium.

2.3 | Practical guide to CLHT

The practical guide to CLHT we present in this paper was devised during several consensus meetings where we integrated the results from the literature review and our survey.

A first version of the guide was presented for validation at a meeting of the Dutch Foundation for Bipolar Disorders (KenBIS). Feedback was also obtained from a nephrologist from our personal network and a psychiatrist who contacted us through the KenBIS website; both were not involved in our study.

3 | RESULTS

3.1 | Review results

Details of our review of the literature are presented in Table 1. In total, we evaluated data on 17 patients described in 14 original articles, all case reports or case series.

In most cases, bipolar disorder or severe unipolar depression were the reasons for lithium use. Other indications were schizoaffective disorder, suicidal ideation and even cluster headaches. The reasons for haemodialysis varied. Although in some cases this was ESKD attributed to lithium nephropathy, several other causes were described, such as glomerulonephritis and rhabdomyolysis. Four articles reported some degree of residual kidney function.

We found differences in dosing strategies. In 15 cases, lithium was introduced in the target dose and then fine-tuned based on pre-dialysis trough levels. In two cases, lithium was started at a lower dose and titrated up guided by blood levels. In one case, the initial dose of 600 mg was followed by a secondary loading dose of 1200 mg. Most articles reported post-dialysis dosing only, with doses usually being taken three times a week. In three cases, lithium was dosed daily.[22–24] Details regarding the type of lithium formulations used were provided in only two case reports.

All articles reported successful therapy, where either remission of psychiatric symptoms was achieved or functioning and quality of life had improved with trough levels of 0.3–1.3 mmol/L. In three cases, the patient eventually received a kidney transplant.[22,23]

Adverse events included thirst, somnolence and dysarthria, with lithium levels ranging from 0.9 to 1.42 mmol/L. In a single case, lithium was discontinued on account of the development of ataxia.[25] None of the articles reported lithium levels of 1.5 mmol/L or higher, the cut-off value taken to indicate clinically significant lithium intoxication.[26]

3.2 | Survey results

3.2.1 | Participant characteristics

Of the surveys returned, 16 were fully completed. Respondents were 10 nephrologists and 6 psychiatrists. Half of the respondents had only treated one CLHT case; one psychiatrist and one nephrologist reported their experiences based on six cases.

TABLE 1 Overview of articles on combined lithium and haemodialysis therapy.

Author, year	Patient characteristics; renal diagnosis; residual kidney function; psychiatric diagnosis	Haemodialysis characteristics	Monitoring	Lithium regimen
Bjarnason[30] et al., 2006	Female, 62 y, 56 kg CKD 0.9 mL/min/1.73 m^3 considered 'no RKF' MDD Severe episode after discontinuation of lithium when first initiating HD	3×/week 3.5 h sessions	Before and after haemodialysis, 3 and 12 h after dialysis during "run-in phase"; 12 h measures used as trough levels	1. 4 mmol post-dialysis 2. Titrated to 16 mmol (=600 mg) in 10 days 3. Reduced to 12.2 mmol No dosing on non-dialysis days Lithium carbonate
Chang[42] et al., 2020	Female, 56 y CKD with anuria BD Manic after discontinuation of lithium due to CKD	Daily HD at start, due to anasarca; 3×/week after 3.5 weeks Session durations NR	Daily monitoring of pre-dialysis levels, later reduced to 3×/week pre-dialysis sampling	1. 400–600 mg daily 2. reduced to 400 mg 3×/week post-dialysis, no dosing on non-dialysis days Lithium carbonate
Engels[22] et al., 2019	Female, 69 y CKD, attributed to lithium use RKF 10 mL/min/1.73 m^3 BD Severe depression after lithium discontinuation at GFR 28 mL/min/1.73 m^3	3×/week 3 h sessions	Pre-dialysis sampling. Additional post-dialysis levels to clarify pharmacokinetic behaviour	1. 300 mg post-dialysis 2. Titrated to 200 mg daily Switch to daily dosing because of significant RKF Lithium carbonate
Grüner[43] et al., 1991	Male, 59 y CKD RKF 200 cc/24 h. BD Manic episode, 1 week after initiating HD	3×/week 4 h sessions	Pre-dialysis sampling 3×/week for 3 months. Reduced to once every 4–8 weeks	1. 600 mg post-dialysis 2. reduced to 450 mg 3. and then 400 mg (10.8 mmol) No dosing on non-dialysis days Lithium carbonate SR
Knebel[37] et al., 2010	Male, 68 y Acute renal failure Rhabdomyolysis Anuria BD Several mood-stabilisers yielded insufficient therapeutic effect or intolerable side effects	3×/week 3 h sessions	Pre-dialysis sampling 3×/week Post-dialysis levels only when investigating signs of possible toxicity	1. 600 mg post-dialysis for 2 years 2. Increased to 900 mg due to hypomania 3. Reduced to 600 mg due to side effects after 1 month No dosing on non-dialysis days Lithium carbonate
Koecheler[23] et al., 1986	$N=2$ Male, 41 y Interstitial nephritis BD. Female, 28 y CKD Diabetic nephropathy Personality disorder, suicidal ideation	3×/week Session durations NR	Pre-dialysis sampling 3×/week	Patient 1300 mg lithium daily Patient 2600 mg post dialysis; no dosing on non-dialysis days Lithium carbonate
Lippman[44] et al., 1984	Female, 65 y CDK Hypertensive nephrosclerosis. RKF insignificant: Serum creatinine 2–2.5 mg/100 mL BD	3×/week Session durations NR HD was started in patient already taking lithium (150 mg/day)	Pre-dialysis sampling, "periodically"	300 mg post-dialysis No dosing on non-dialysis days Lithium formulation NR
Port[25] et al., 1979	Male, 53 y CKD Nephrosclerosis RKF NR BD Severe depressive episode at start of dialysis followed by manic episode, not adequately responding to antipsychotics	3×/week 4 h sessions	Pre-dialysis sampling 3×/week Additional post-dialysis for research purposes	1. 600 mg single starting dose post-dialysis 2. 300 mg 3. 600 mg 4. 900 mg No dosing on non-dialysis days Lithium carbonate

Lithium levels; clinical outcomes; adverse effects	Take home messages
1. NR 2. ±0.9 mmol/L Uncomfortable thirst 3. ±0.7 mmol/L Effective and well tolerated	A method based on volume of distribution (Dose = ⅓V_d × C) was found to be accurate in predicting an adequate maintenance dose A loading dose based on this model would have resulted in toxic C_{max}
1. 0.5–1.2 mmol/L 2. 0.3–0.4 mmol/L Total resolution of manic symptoms after 6 weeks and for 2 years follow up No adverse events reported	Lower than usual target concentrations are suggested, e.g. 0.6 mmol/L for mania Authors advise daily monitoring for 2 weeks, followed by 3×/week pre-dialysis sampling until a steady level is reached. After that, once per 3 to 12 months
1. 0.16–0.33 mmol/L 2. 0.6 mmol/L Fluctuating between 0.16 and 1.01 mmol/L during follow-up Remission of depression No adverse events 1-year follow up, whereafter kidney transplant	Starting dose = maintenance dose as estimated following the model by Bjarnason et al. Titration from there on, guided by blood sampling Authors advise taking residual kidney function into account
1. 0.7 mmol/L 2. NR 3. 0.45–0.7 mmol/L Effective treatment of manic symptoms up until 3-year follow up Significant rise of PTH and decrease of serum calcium	Target dose estimation based on averages of earlier studies: Dose = 18 mmol (667 mg) × C. Lower than usual target level suggested: 0.6–0.9 for mania. Consider fluctuations due to changes in Vd, small variations in session length and loss of lithium through sweating
1. 0.6–0.8 mmol/L 2. 0.84–1.42 mmol/L 3. 1.41 mmol/L, dropping to 0.75 mmol/L Two episodes of hypomania and one manic episode occurring over 2 years: significant improvement compared to prior course Somnolence and slurred speech at 1.42 mmol/L	Lithium levels remained elevated until after three dialysis sessions following dose reduction, attributed to redistribution Possible higher susceptibility to toxicity, at levels <1.5 mmol/L, in dialysis patients is suggested
Patient 1 1.3 mmol/L Patient 2 1.0 mmol/L Both patients received renal allograft Psychiatric outcomes and adverse effects NR	Switching back to daily lithium dosing after kidney transplant: Postoperative ATN requiring 1–2 weeks of HD is common. Authors suggest starting 300–600 mg doses post-dialysis, continuing to a daily or twice daily 300 mg dosage when renal function returns, followed by titration depending on renal function achieved.
1. 0.5–0.6 mmol/L Depressive relapses annually; Higher level of functioning than prior to lithium therapy during 3-year follow-up Adverse events NR	Authors advise closer than usual clinical and laboratory monitoring
1. 0.2 mmol/L 2. 0.3–0.4 mmol/L 3. 0.5–0.8 mmol/L 4. ~1.0 mmol/L Euthymia after 4 weeks Lithium discontinued due to adverse events: mild ataxia, broad-based gait	Authors address the possible discrepancy between peak levels and pre-dialysis levels as an explanation for lithium toxicity Directly post-dialysis administration of lithium is described as an advantage, as adherence can be controlled by dialysis-unit personnel

(Continues)

TABLE 1 (Continued)

Author, year	Patient characteristics; renal diagnosis; residual kidney function; psychiatric diagnosis	Haemodialysis characteristics	Monitoring	Lithium regimen
Procci[36] et al., 1977	Female, 25 y CKD GlomerulonephritisRKF insignificant BD Acute mania	3×/week 5 h sessions	Pre-dialysis sampling; frequency NR	1. 300 mg post-dialysis 2. 450 mg within a week 3. 600 mg after 2 months No dosing on non-dialysis days Lithium carbonate
Quentzel[31] et al., 1997	Male, 44 y CKD RKF NR Schizo-affective disorder Manic episode	3×/week Session durations NR	Pre-dialysis sampling 3×/week	1. 600 mg post-dialysis 2. 1200 mg 3. 900 mg No dosing on non-dialysis days Lithium formulation NR
Topp[45] et al., 2021	Male, 57 y CKD Lithium-induced nephropathy BD Manic episode	3×/week Exact session durations NR. Patient did not tolerate optimal dialysis hours	Pre-dialysis sampling 3×/week	1. Titration using steps of 100 mg post-dialysis, during 12 weeks 2. 600 mg No dosing on non-dialysis days Lithium carbonate SR
Walcher[33] et al., 2002	Sex NR, 60 y CKD RKF: 300–500 mL/24 h Creatinine clearance 1.4 mL/min MDD	3×/week 4.5 h sessions	Pre-dialysis sampling 3×/week for 2 weeks; Afterward weekly until steady stage; Monthly monitoring during maintenance phase Additional post-dialysis measures suspecting intoxication	1. 536 mg post-dialysis 2. 1608 mg after 1 week No dosing on non-dialysis days Lithium acetate
Zetin[32] et al., 1981	*N* = 3 Male, 57 y Male, 68 y Female 68 y ESKD No RKF Psychiatric diagnoses NR	3×/week Session duration NR	Pre-dialysis sampling, weekly	1. 300 mg post-dialysis for 1 week 2. 600 mg No dosing on non-dialysis days Lithium carbonate
Zuddas[24] et al., 2015	Male, 54 y ESKD RKF NR Cluster headaches	3×/week 5 h sessions	Pre-dialysis sampling 3×/week	1. 150 mg pre- and post dialysis in addition to 150 mg on non-dialysis days. 2. After 5 days: 150 mg directly post-dialysis, 150 mg in the evening post-dialysis and 150 mg every morning on non-dialysis days No reason reported for daily dosing Lithium carbonate

Abbreviations: BD, bipolar disorder; CKD, chronic kidney disease; CLHT, combined lithium and haemodialysis therapy; ESKD, end-stage kidney disease; GFR, glomerular filtration rate; HD, haemodialysis; MDD, major depressive disorder; NR, not reported; RKF, residual kidney function; SR, slow release; y, years of age.

3.2.2 | General approach

Only three respondents reported having a standard practice, of whom only one (a psychiatrist) used a written CLHT protocol.

3.2.3 | Collaboration

All respondents reported having consulted another specialist (psychiatrist or nephrologist) prior to initiating the concurrent treatment. About half (47%) had also consulted a pharmacist. In nearly all cases, the psychiatrist-nephrologist consultation occurred ad hoc. Only one respondent described a routine meeting with a nephrologist, while three others pointed to logistic barriers for such a consultation. All other respondents deemed ad-hoc consultations sufficient (and described these as the most easily accessible).

Four (24%) respondents reported not having initiated an interdisciplinary consultation when the dialysis schedule was changed, stating that both the psychiatrist and the nephrologist could alter the lithium prescriptions independently. Most other (*n* = 10) respondents

Lithium levels; clinical outcomes; adverse effects	Take home messages
1. 0.34 mmol/L 2. 0.57–0.7 mmol/L 3. 0.65–0.79 mmol/L Remission of psychiatric symptoms within 2 weeks and during 26-week follow-up Adverse events NR	Authors suggest that lower serum levels could be pursued for mania
1. Barely detectable, measured after one dose 2. 1.4 mmol/L, again after one dose 3. 0.8–1.0 mmol/L Remission was reached after 1.5 weeks Adverse events NR	The authors suggest a loading dose to achieve rapid control in urgent cases.
1. <0.4 mmol/L 2. 0.4–0.6 mmol/L	A low starting dose is advised in patients that do not tolerate optimal dialysis durations
1. NR 2. 0.6 and 0.8 mmol/L Effects on psychiatric symptoms NR Follow-up was 40 weeks No adverse events	The impact of RKF is discussed. Creatinine clearance might not reliably reflect residual renal lithium clearance Authors underline the effect of HD session duration on lithium clearance, and hence the dosage needed Bicarbonate HD might reduce rebound effect
1. 0.2–0.5 mmol/L, respectively 2. 0.5–0.9 mmol/L Lithium was tolerated well; no signs of toxicity Clinical outcomse NR	Patients with bipolar affective disorder should not be denied lithium treatment
1. 0.13–0.17 mmol/L 2. 0.45–0.58 mmol/L Complete recovery from headaches was obtained No adverse events	CLHT has added value outside psychiatry. In this case the treatment of cluster headache

mentioned the psychiatrist as the specialist responsible for changes in lithium dosing.

3.2.4 | Initiating CLHT

Determining the initial lithium dose

When starting lithium in patients already on haemodialysis, the majority ($n = 9$) of the respondents reported having started with a low dose of lithium for their patients on haemodialysis, titrating the dose based on subsequent serum levels. One had started with the target dose as determined based on the volume of distribution. One psychiatrist highlighted the importance of the psychiatric diagnosis, which could imply the need to start off with higher doses in urgent cases. Others had refrained from answering this question because of a lack of experience. When starting haemodialysis in patients already using lithium, seven respondents described having adopted a slow titration regimen, while nine stated to have continued with the target dose or having adjusted the dose according to serum lithium levels.

When to dose

All respondents stated to have been administered lithium immediately or several hours after dialysis. Interestingly, seven respondents, including five nephrologists, routinely dosed on non-dialysis days as well. Six respondents only dosed on non-dialysis days in case of significant residual diuresis, while four never did.

When lithium was (to be) used on non-dialysis days, seven respondents, six of whom were nephrologists, reported prescribing equal doses on dialysis and non-dialysis days. Four others described using a primary post-dialysis dose followed by lower doses in the days between dialysis sessions.

Therapeutic drug monitoring during the initiation phase

All but one respondent described measuring lithium levels directly pre-dialysis. Six respondents recounted they also measured serum levels after the session, either several hours or a day post-dialysis. One described taking routine daily measures. Three respondents reported lower-than-usual target trough levels, while all others used standard target concentrations.

3.2.5 | Continuation of concurrent treatment

Frequency of trough level monitoring during the maintenance phase

Seven of our respondents marked reaching the target dose as the start of the maintenance phase. Others relied on stable trough levels for a minimum of three measurements before reducing the frequency of testing. Two respondents continued testing before every dialysis session and three others adhered to weekly tests, while most reduced the test frequency to once a month.

Additional measurements

The most reported reasons for additional lithium level testing were changes in the dialysis schedule, changes in psychiatric symptoms, the occurrence of adverse effects possibly attributable to lithium, changes in comedication and changes in residual diuresis.

4 | DISCUSSION

4.1 | Main finding

Although not often applied, lithium and haemodialysis treatment can be safely combined with—apparently—generally favourable outcomes.[18] Since the question of how CLHT should be delivered is beyond the scope of current guidelines, with this study we combined the evidence of its use and effectiveness from published reports with a survey of current practices among nephrologists and psychiatrists to arrive at an integral, best practice guideline for the initiation and maintenance of CLHT (summarised in the flowchart in Figure 2), offering practical recommendations (see Table 2). In doing so, we hope to have broken down some of the barriers to applying the combination treatment.

4.2 | Limitations

We merely identified 14 original articles fit for review, with findings being limited to case reports and case series, rendering it impossible to derive sound, evidence-based guidelines from the evidence reported and were hence confined to offering practice-based recommendations.

Also, there is a risk of publication bias: cases that did not respond well to CLHT may be less likely to be reported in the literature. It should also be mentioned that sample size of our survey is small, possibly due to low response rate and low prevalence. We were only able to include 16 respondents. Our survey was a national survey in the Netherlands, which limited the number of possible respondents.

Although we went to great lengths to recruit as many nephrologists and psychiatrists as possible for our survey, it is likely that our method was insufficient to reach all specialists that met our inclusion criteria, i.e., having experience with CLHT. It is likely that only those with a clear affinity with the therapy will have made the effort to answer our calls. Be that as it may, having a pronounced affinity with the subject may also imply having expert knowledge, lending strength to our analysis and recommendations. However, we mostly gathered information on the regimens chosen without specifically inquiring into the underlying rationale for these choices.

4.3 | Clinical implications

Lithium sometimes is the only effective treatment for specific patients, preventing severe mood episodes. With CLHT, once mood is stabilised, kidney transplant becomes feasible in patients previously unfit for this procedure.[22,23] Lithium delivery around and after kidney transplant is an option and is associated with its own specific complexities, which are beyond the scope of this paper.[23,27,28]

It is unfortunate that CLHT is little known and even less opted for. During our recruitment efforts we came across several colleagues who were unaware of the possibility of CLHT. This underscores the need for clear guidelines and more evidence. In the absence of the latter, we think that nephrologists and psychiatrists can benefit from the easy-to-use tool for CLHT delivery we present in this paper.

Knowing about the possibility of CLHT is relevant when doctors and patients are first confronted by declining renal function during lithium use, so ahead of ESKD. In view of the psychiatric risks, it might even be considered not to discontinue lithium altogether.[13,14] If lithium is discontinued during this phase, the possibility of restarting the therapy should be reviewed regularly. In a previous publication we made several more recommendations on managing renal decline during lithium use.[9,29]

Next, we will discuss in more detail the different aspects of CLHT, to what extent the data from our review and survey correspond and the considerations behind our flowchart and recommendations.

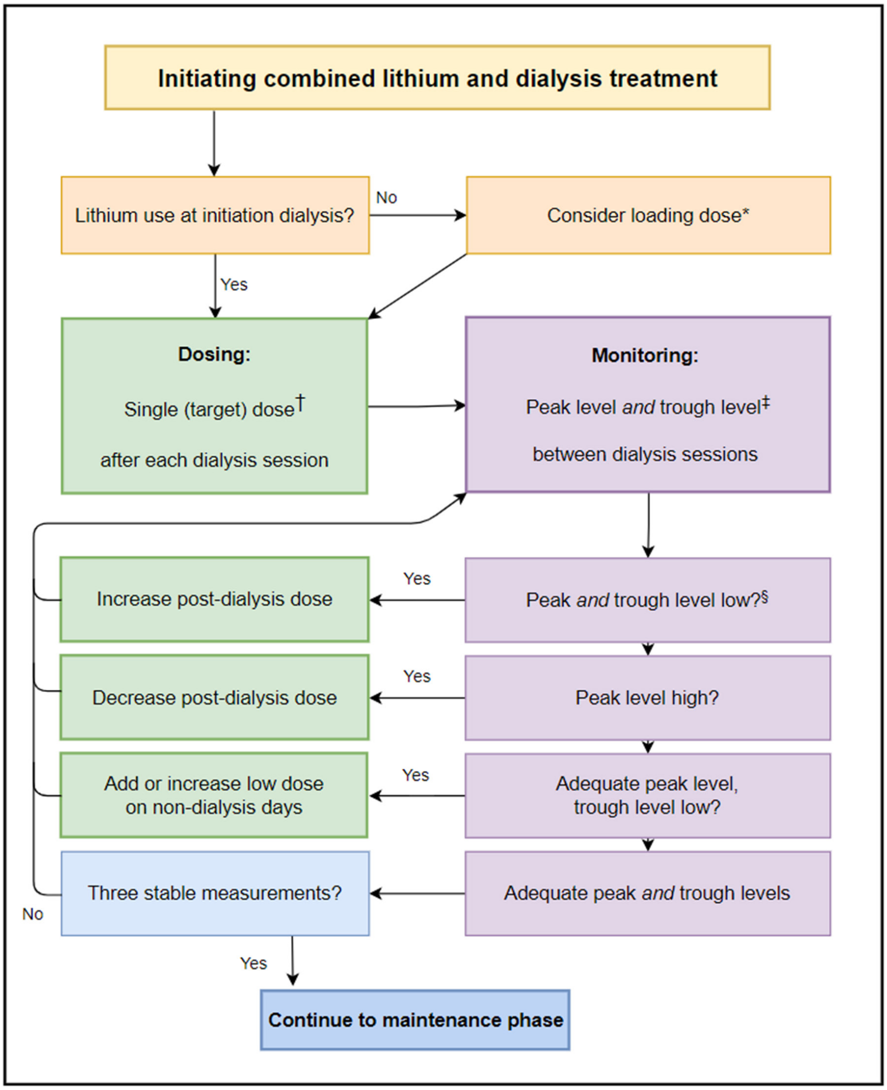

FIGURE 2 Flowchart for the initiation of concurrent lithium and haemodialysis treatment (CLHT). *Loading dose: e.g. 800 mg in urgent cases (e.g. manic episode or high risk of suicide); †Target dose (mg) = 10 × body weight (kg) × target concentration (mmol/l); ‡Peak levels (e.g.) measured day after dialysis, trough levels measured pre-dialysis; §Target concentrations depend on the indication.

4.4 | General approach and collaboration

The necessity of the nephrologist and psychiatrist working closely together in case of CLHT seems evident. However, we found very little consensus on how this multidisciplinary collaboration should be organised. In our own clinical experience, a routine meeting between the two specialists permits the low-threshold exchange of information, allowing both to build expertise and shared responsibility, enabling them to reach consensus when decisions need to be made, especially when these go beyond current guidelines.

4.5 | Delivering initial CLHT

During dialysis most of the lithium present in the extracellular compartment (plasma, interstitial fluid, etc.) is extracted.[18] Assuming no significant elimination of lithium between dialysis sessions, each session can be followed by a single dose of lithium sufficient to replace the amount of lithium that has been cleared during dialysis.[30] In general, this applies both to patients taking lithium when starting dialysis and to dialysis patients starting lithium therapy.

However, lithium pharmacokinetics follow a two-compartment model of distribution.[30] Patients who are already on lithium at the start of dialysis will still have lithium in the peripheral compartment (poorly perfused tissues) after a dialysis session, so steady state is likely to be reached relatively quickly. Vice versa, it may take longer to reach steady state when initiating lithium in patients already on haemodialysis. This is especially relevant when time is a crucial factor. In urgent cases, such as during manic psychosis, a loading dose may help to reach steady state more quickly,[31] although this does carry a risk of toxic peak levels.[30]

Although in theory immediate release (IR) tablets could be preferred over sustained release (SR) formulations so that lithium dialysed from the serum is replaced as quickly as possible, we do not have enough data to support a preference for a particular formulation. We believe it is unlikely that there would be a major difference in efficacy. Therefore, we recommend making the usual considerations regarding tolerability and available dosages.

TABLE 2 Practical guide to concurrent lithium and haemodialysis treatment (CLHT).

General principles

- CLHT should be considered in patients with severe mood disorders and (imminent) end-stage kidney disease even when lithium was previously discontinued on account of declining renal functions
- CLHT is a shared responsibility requiring continuous multidisciplinary finetuning
- Low-threshold consultations between nephrologist and psychiatrist are mandatory
- Routine multidisciplinary meetings are advised to inform each other and reach consensus when decisions need to be made that go beyond current guidelines
- Patients should be treated in settings allowing easy interdisciplinary collaboration to minimise the burden for the patient
- Shared amenities like a clinical laboratory and electronic patient records are recommended

Shared decision making

- Patients and their principle caregivers should be informed timely and clearly of the possibilities and implications of CLHT
- Discuss the pros and cons of all relevant options (e.g. continuing, tapering or switching lithium to an alternative mood stabiliser)
- Since the patient needs to incorporate the advice from multiple experts, try to avoid inconsistencies; shared decision making with all experts present is recommended

Starting lithium in patients on haemodialysis

- See the flowchart in Figure 2 for how to initiate CLHT
- The target dose (mg) can be determined as follows: 10 × body weight (kg) × target concentration (mmol/L)
- The target dose can be used as a starting dose; it does not appear to be necessary to titrate up to the target dose
- As a standard, lithium (IR or SR) is taken on dialysis days only, immediately after dialysis
- Prescribing lithium on non-dialysis days may be necessary in cases with residual diuresis
- It is recommended to initiate CLHT in a clinical setting both for pragmatic and for safety reasons
- Trough levels are to be assayed before each dialysis session until concentrations are stable for at least three consecutive measurements, before reducing monitoring frequency

Continuing concurrent treatment (maintenance phase)

- Trough lithium levels can be obtained directly pre-dialysis
- Frequent—at least monthly—trough level measurements are recommended
- Lithium therapy should be delivered and monitored by the treating psychiatrist
- Changes in psychiatric symptoms should be monitored closely, preferably using a relapse prevention plan
- Additional lithium measurements are advised in case of changes in dialysis schedule, residual diuresis, adverse effects, changes in co-medication, fluid intake, warm weather, and other potentially relevant events
- Consider whether kidney transplant is feasible once mood is stabilised

The following method for estimating the lithium maintenance dose (D), based on the volume of distribution (V_d) and target concentration (C), was described by Bjarnason et al. (2006):

$$D \text{ (in mmol)} = V_1 \text{ (in l)} \times C \text{ (in mmol/l)}$$

V_1 is the volume of distribution in the central compartment.
V_1 for lithium has been estimated to be ⅓ of the total V_d[43].
The weight normalised V_d for lithium is approximately 0.8 l/kg[44], which means that:

$$V_d \text{ (in l)} = 0.8 \times \text{body weight (in kg)}$$

and:

$$V_1 = ⅓ \times 0.8 \times \text{body weight}$$

Now, the dose can be calculated according to body weight:

$$D \text{ (in mmol)} = ⅓ \times 0.8 \times \text{body weight} \times C$$

Finally, the dose can be expressed in milligrams.
Lithium carbonate contains 0.027 mmol/mg lithium (Li+) ions[45], which means that:

$$D \text{ (in mg)} = ((0.8 \times ⅓) / 0{,}027) \times \text{body weight} \times C$$

and:

$$\mathbf{D \text{ (in mg)} \approx 10 \times \text{body weight (in kg)} \times C \text{ (in mmol/l)}}$$

FIGURE 3 Rule of thumb for lithium target dosing explained.

Our survey revealed that most of the respondents started patients off on an extra low dose, titrating up from there, which contrasted with practices reported in the literature we reviewed. Taking the results of these case reports into account, we suggest that starting with the target dose appears to be safe and prevents wasting precious time and prolonged suffering. Again, this applies both to patients taking lithium when starting dialysis and to dialysis patients starting lithium therapy.

But how does one determine the target dose? Authors suggested several estimation methods, ranging from rather complicated calculations[32] to always starting with 600 mg post-dialysis.[33] We propose the use of the following formula:

$$10 \times \text{body weight (in kg)} \times \text{target concentration (in mmol / L)} = \text{target dose (in mg)}.$$

Our rule of thumb takes into account body weight as a derivative of the volume of distribution (see Figure 3) and has the advantage of being both pragmatic and patient specific.

In actual practice, residual renal function is quite common in lithium-induced nephropathy.[18] This means that in-between dialysis treatments some amount of lithium is still cleared by the kidneys. When the residual function is significant, a single-dose regimen can lead to fluctuating lithium concentrations and insufficient trough levels[22] or toxic peak levels to obtain the desired trough levels.

Therefore, determining additional peak levels is advised, at least when initiating CLHT. This way, toxic levels of 1.5 mmol/L or higher can be prevented or readily detected. An interesting question is when these peak levels should be measured. The time to reach the maximum concentration for lithium carbonate typically is between 1.5 and 3 h. However, due to rebound redistribution and the presence or absence of residual renal function, this is different in dialysis patients. We hence suggest determining peak levels the morning after dialysis. Moreover, for both practical and safety reasons, it is advisable to admit patients to a medical psychiatry unit during the CLHT initiation phase when available and feasible for the patient.

Interestingly, although significant residual renal function would be a valid reason for daily lithium administration, this was rarely the case in the literature we reviewed, whereas in the respondents of our survey daily dosing was common (11/16). To our surprise, seven physicians even reported standard daily dosing regardless of residual renal function. Unfortunately, we did not include any questions as to why this was.

As to lithium dosing on non-dialysis days, there are two options: giving a low dose supplement each day or use evenly divided daily doses. Most of our respondents opted for the latter regimen, which also surprised us as, theoretically, this results in larger peak-to-trough fluctuations (serum levels rising between dialysis days). On the other hand, one might argue that evenly dividing the doses is patient-friendly and reduces the risk of medication errors or non-adherence. Engels et al.[22] reported a case in which 200 mg daily resulted in both peak and trough levels being between target values.

Partial non-compliance is common among patients with bipolar disorder.[34] The prior method can therefore have an additional benefit when the primary post-dialysis dose is administered at the dialysis facility, diminishing the risk of sub-therapeutic blood levels. If this dose is missed, it should always be replaced. This does not apply to the smaller doses on non-dialysis days, as renal impairment leads to higher risks of developing lithium intoxication. A partial replacement dose can be considered.[35]

As to the issue of target trough (i.e., pre-dialysis) concentrations, it is important to note that commonly used target concentrations in regular lithium treatment are based on twice-daily doses, but pharmacokinetics are very different in patients receiving haemodialysis. Nevertheless, the target levels that were used were generally the same as used in routine, stand-alone lithium treatment, seemingly without problem. Some of the authors and survey respondents suggested lower target levels.

4.6 | Continuing CLHT

Little consensus exists on when to proceed to a continuation or maintenance phase in CLHT during which the frequency of lithium measurements is reduced. Since lithium follows a two-compartment model of distribution, a rebound effect after dialysis can occur, resulting from drug redistribution from the intracellular to the extracellular compartment, and affecting the time to reach a steady-state concentration after each dose change.[36,37] It seems reasonable to postpone cutting down the frequency of measurements until lithium concentrations are stable for at least three consecutive measurements.

There also was little consistency regarding the frequency of lithium measurements during the maintenance phase. On average, serum levels were determined more frequently than in regular lithium treatment, possibly because of the exceptional nature of CLHT. Most of our respondents adopted monthly testing, which seems reasonable, although less frequent measurements might be justifiable given the expected pharmacokinetic stability once CLHT has been established.

Additional measurements are needed when the dialysis schedule is changed or when residual kidney function decreases, where low-threshold consultations between psychiatrist and nephrologist are vital. As in regular lithium therapy, additional measurements are also indicated when there are changes in lithium dosing or psychiatric symptoms, in case of indications of toxicity, significant changes in fluid intake (e.g., due to stomach flu), alterations in medication that might interact with lithium, and changes in weather that might significantly affect sweating.

4.7 | Research implications

Our study is far from exhaustive and mostly based on case reports and expert opinions. Many questions remain. Is daily dosing advisable when there is no evidence of residual diuresis? How often should lithium blood levels be measured during the CLHT maintenance phase? What should be the strategy in case of peritoneal dialysis? What would be the influence of sodium polystyrene sulfonate, which binds lithium?[38] Yet, conducting prospective studies would seem extremely difficult given the paucity of CLHT. International collaboration resulting in surveys with larger sample sizes could help improve our knowledge on this subject. Ideally, national or preferably international registers should be set up that can foster the collection and bundling of data.

5 | CONCLUSION

Based on a multicentre survey and a review of the literature, we argue that CLHT appears to be both safe and effective, provided that the treating psychiatrist and nephrologist share the responsibility for all relevant therapeutic decisions, with the treatment requiring continuous multidisciplinary finetuning.

To lower the barriers for its use, we provide a flowchart showing how to initiate lithium therapy in dialysis patients and have formulated practical guidelines for the combined therapy, including a rule of thumb for the lithium target dose.

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DATA AVAILABILITY STATEMENT

Research data are not shared.

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