Low dose lithium treatment in patients with mental illness

A systematic review

Version 2

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Abstract

Introduction: Lithium is widely used in bipolar disorder and major depression with good results. But at recommended serum concentrations of 0.5-0.8mmol/L, side effects such as polyuria, tremor and hypothyroidism often occur despite strict monitoring. Clinical experience indicates that lower concentration reduces side effects and still may maintain a therapeutic effect. Studies have shown a neuroprotective effect of lithium that may benefit e.g. patients with Alzheimer's disease. Early studies have shown positive results treating irritable patients with lithium in microdoses.

Objective: The objective was to gather and analyze the available peer reviewed and published clinical trials on PubMed regarding lithium treatment and mental illness, in doses and/or at concentrations lower than those generally considered therapeutic. Articles regarding bipolar patients in a manic phase were excluded. The outcome measures were quantitative data on depressive symptoms, mood and/or cognitive function.

Material & Methods: PubMed’s database, reviews and references in included articles were screened. The PubMed search was conducted 2017-10-22. “low dose”, “low dosage”, “subtherapeutic”, “microdose”, “nutritional”, and “dementia” together with “lithium” gave 1496 results and 135 clinical trials.

Results: Eight articles were included in the study. Two of three studies about dementia/aMCI found positive results on cognitive function. All three studies about major/refractory depression found a positive result with lithium augmentation. Both articles about irritability in former substance abusers found positive results with lithium treatment.

Conclusion: The evidence supports that low dose and microdose lithium could be useful treatments in dementia, depression and irritability. Further research is necessary to consolidate these findings.

Key Words: Lithium, dementia, aMCI, depression, augmentation, irritability, low dose, microdose, systematic review.
Abbreviations

AD – Alzheimer’s disease
ADAS-cog – Cognitive subscale of the Alzheimer’s Disease Assessment Scale
aMCI – amnestic mild cognitive impairment
CGI-S – Clinical Global Impression- Improvement Scale
CSF – Cerebrospinal fluids
DSM – Diagnostic and Statistical Manual of Mental Disorders
HDRS – Hamilton Rating Scale for Depression
MADRS – Montgomery-Åsberg Depression Rating Scale
MeSH – Medical subject headings
MMSE – Mini Mental State Examination test
MSRS – Manic State Ratings Scale
NPRU – Naval Psychological Research Unit Mood Scale questionnaire
p-tau – Phosphorylated tau proteins
RCT – Randomized controlled trial
SNRI – Selective serotonin-norepinephrine reuptake inhibitors
SSRI – Selective serotonin reuptake inhibitors
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Introduction

In 1949 John Cade published an article where he successfully treated manic patients with lithium salts [1]. In the 70’s these results were confirmed, and lithium was also proven to be useful as a prophylactic for bipolar patients [2]. The most common lithium salt used in medication is lithium carbonate, but in Sweden lithium sulfate is mostly used. Lithium has since then been used widely against bipolar disorders and major depressions with good results, and it is the first drug of choice for bipolar affective disorders [3]. The second drug of choice is antiepileptic medication, e.g. Lamotrigine, Valproate and Carbamazepine. In some cases, antipsychotic pharmaceuticals are used [4].

But even in therapeutic concentrations (0.5-0.8mmol/L) and strict supervision, side effects such as polyuria, tremor and hypothyroidism are common in lithium treated patients. Other well described side effects include lithium intoxication, nephrotoxicity, hypercalcemia, hyperparathyroidism, effects on the fetus and weight gain [5]. Clinical experience indicates that lower concentration reduces side effects and still may maintain a therapeutic effect. The therapeutic effects and side effects of lithium are well described in the literature. To the author’s and supervisor’s knowledge, however, the evidence for low dose treatment is relatively undescribed.

Lithium and dementia

Alzheimer’s disease (AD) is the most common dementia, with a prevalence of 19.4 per 1000 person-years among European people 65+ [6]. There are some symptomatic treatments available with various response, but no approved drug that alters the progression of the disease. The hallmarks of AD include hyperphosphorylated tau proteins and amyloid-beta plaques. Amnestic mild cognitive impairment (aMCI) is regarded as a pre state for dementia [7,8]. Studies have shown a neuroprotective effect of lithium that benefits e.g. patients with Alzheimer's disease [9,10]. Several recently published data have discovered that bipolar patients treated with lithium have a lower incidence of dementia [11,12].

Lithium has been shown to inhibit the activity of glucogensynthase-kinase 3α and β (GSK-3α, GSK-3β), which are enzymes theorized to play a major role in the pathogenesis of AD [13]. GSK-3α and GSK-3β hyperphosphorylates tau proteins that gives neurofibrillary tangles, and contributes to producing amyloid plaques [14,15]. In rodents and in in vitro studies, lithium has been proven to induce brain-derived neurotrophic factor (BDNF) [16,17].
Mauer et al. published a review 2014, looking deeper into the possible connection between lithium and neuroprotection in AD, with mixed results [18]. One possible explanation for this is the side-effect burden of higher lithium concentrations, which elderly AD patients are more prone to, due to higher fat mass in relation to lean mass, lower glomerular filtration and polypharmacy [19,20].

**Lithium and depression**

Lithium is a well-known mood stabilizer, recommended as first-hand treatment of bipolar disorder. Ecological studies have showed reduced risks for depressions and suicides in areas with naturally lithium rich groundwater supplies [21]. This indicates that lithium has some therapeutic effect even in microdoses.

Lithium augmentation (i.e. to add lithium to standard antidepressant medication) in refractory depression is well described in the research literature, and one of the most efficient available strategies [22,23]. However, there is less support for lower concentrations of lithium in refractory depression [24]. Complex pathogenesis and general therapy resistance could be an explanation, but this may also constitute an under-researched area. To the author’s and supervisor’s knowledge, there are no placebo controlled studies regarding low dose lithium treatment in refractory depression.

**Lithium and irritability**

Irritability is somewhat undefined, and not a diagnosis by itself in DSM-5. However, it is a common symptom together with depression, and irritability is included as diagnostic criteria in various diagnoses in the Diagnostic and Statistical Manual of Mental Disorders (DSM) e.g. generalized anxiety disorder, borderline personality disorder and nicotine withdrawal [25–27].

Early studies have analyzed if irritability can be treated with lithium, especially in former or active substance abusers [28–30]. To get a deeper understanding of low dose lithium treatment and its potential usage, it is important to analyze the evidence in different fields of study, where irritability is a well-known indication for psychiatric treatment.

**Objective**

The objective for this review was to gather and analyze the available peer reviewed and published clinical trials on PubMed’s database regarding lithium treatment and mental illness, in doses and/or concentrations below what generally is considered therapeutic.
Aim
The aim of this review was to investigate the evidence for treating patients with symptoms or diagnosis of dementia, depression or irritability with lithium serum concentrations <0.5mmol/L.

Material & Methods

Literature search
This study was conducted as a systematic review with searches on PubMed’s database. The search was augmented with cross-referencing from included articles and selected reviews by Bauer et al (2010) and Mauer et al (2014) (Figure 1) [18,24].

In 2017-10-22 were search words “low dose”, “low dosage”, “microdose”, “nutritional”, “subtherapeutic” or the MeSH term “dementia” combined with the MeSH term “lithium”. Of the 135 clinical trials, 119 articles were excluded after screening the abstracts. 76 of the excluded articles were about lithium related side effects or diseases unrelated to the aim of this review e.g. kidney and thyroid disease, HIV, Huntington’s chorea, stroke or cancerous tumors. The remaining 43 abstracts were excluded due to lithium concentrations >0.5mmol/L in depression, dementia or bipolar disorder. (Figure 1).

Inclusion criteria
The population for this review consisted of adults, both men and women, with diagnosis or symptoms of dementia, depressive disorder or irritability.

The intervention was treatment with lithium that gave a serum concentration below 0.5mmol/L. Doses well below noticeable serum concentration were also included.

The control was other antidepressants, mood stabilizers or placebo. Observational open label, non-randomized studies were also included due to the limited number of RCT.

The outcome measures were quantitative data on depressive symptoms, mood and/or cognitive function.

Exclusion criteria
Patients with bipolar disorders in a hypomanic, manic or mixed phase, not being diagnosed with a depressive phase, were excluded. Trace water- and epidemiological studies were excluded, due to not meeting up to the criteria of active lithium treatment. Case reports were excluded, due to not being active trials.
Lithium augmentation articles were excluded if there were more interventions/augmentations apart from lithium and not placebo controlled. Articles in other languages than English were excluded.

Figure 1. Flowchart of the conducted search on PubMed’s database, with references and reviews.
Ethics
All included studies were peer reviewed and published. All included studies had applied for and were granted ethical approvals in accordance with the Helsinki declaration. Not all studies mentioned an ethical approval, but had been published and included in the PubMed database. Thus, having a high probability that ethical approval was already applied for and granted, just not mentioned.

Quality assessment
The quality assessment was determined through the Grading of Recommendations Assessment, Development and Evaluation (GRADE) questionnaires, downloaded from the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) [31]. The aim was to evaluate the risk for bias in the studies, after assessing the selection bias (A1), performance bias (A2), detection bias (A3), attrition (A4), reporting bias (A5) and other considerations (A6). This gave a combined evaluation of low (L), average (A) or high (H) risk for bias (Table 2).

The conducted search was examined by both the author and supervisor, and cross-referenced with published systematic reviews regarding lithium treatment in dementia and depression. The grading of the articles was consolidated with the supervisor, but conducted by the author alone. The inclusion and exclusion criteria were reported to the examiner before the conducted search, and only small clarifications and adjustments were made during the search-phase of the review.

Results
A search on PubMed’s database was conducted. 1496 results were found, 916 were on human species, and 135 of those were clinical trials in English. 16 articles were selected after the reading of the abstracts of the 135 clinical trials, they were read in full text. Seven of them were included in the study. After cross-referencing with reviews in the field of study and references in included articles, one more article was included (Figure 1).

Three articles were about dementia or cognitive impairment, three were about depression and two about irritability in former substance abusers (Table 1). Two of the articles had a high risk for bias, four had an average risk for bias and two had a low risk for bias. Five articles were RCT, two were observational open label, and one was observational dose-response (Table 2). Almost every included article had different outcome measures and quantitative tests (Table 1).
Mini Mental State Examination test (MMSE) is a screening method for cognitive functions, well used in clinical practice [32]. The Clinical Dementia Rating scale (CDR), as well as Cognitive Subscale of the Alzheimer’s Disease Assessment Scale (ADAS-cog) and Consortium to Establish a Registry for Alzheimer’s Disease Delayed recall test (CERAD) are different well established cognitive tests for dementia patients, often used in medical research studies [33–35]. The Clinical Global Impression- Improvement Scale (CGI-S), Montgomery-Åsberg Depression Rating Scale (MADRS) and Hamilton Rating Scale for Depression (HRSD) are well established rating scales for depression symptoms [36–38]. The Naval Psychological Research Unit Mood Scale questionnaire (NPRU) and Manic State Ratings Scale (MSRS) are not often used in clinical practice, and measures mood after sleep deprivation (NPRU) and symptoms of mania (MSRS) [39,40]. The scales include symptoms of irritability and grade of general well-being, which are of essence diagnosing patients with substance abuse.
Table 1. Overview of the analyzed trials

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study type, Study time</th>
<th>Study population</th>
<th>Intervention/Exposure Subjects(S), Control(C)</th>
<th>Outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nunes et al, 2013 [41]</td>
<td>RCT double-blind, 15 months evaluation.</td>
<td>113 patients with AD, scoring 9-21 on MMSE.</td>
<td>S=300µg lithium carbonate/gluconate (n=58) C=Placebo (n=55)</td>
<td>MMSE score.</td>
</tr>
<tr>
<td>Forlenza et al, 2011 [42]</td>
<td>RCT double-blind, 12 months.</td>
<td>45 patients with aMCI.</td>
<td>S=Lithium carbonate, 0.25-0.5mmol/L (n=24) C=Placebo (n=21)</td>
<td>CDR, ADAS-Cog, CERAD, CSF biomarkers.</td>
</tr>
<tr>
<td>Macdonald et al, 2008 [43]</td>
<td>Open Label Observation al, up to 1 year.</td>
<td>22 patients with mild to moderate AD, MMSE 12-24 points.</td>
<td>S= Lithium carbonate, 0.4mmol/L (n=8-22) C=AD cohort register, equal MMSE score.</td>
<td>MMSE, ADAS-cog.</td>
</tr>
<tr>
<td>Alevizos et al, 2012 [44]</td>
<td>Open label observation, 6 weeks.</td>
<td>47 patients with unipolar (n=33) or bipolar (n=14) depression, unresponsive to Venlafaxine.</td>
<td>S=Venlafaxine 5mg/kg +lithium carbonate, 0.33mEq/L. (n=47) No control group.</td>
<td>CGI-S</td>
</tr>
<tr>
<td>Wilkins on et al, 2002 [45]</td>
<td>RCT double-blind, 2 years.</td>
<td>49 elderly patients (mean age 75.8) without dementia, recovering from major depression.</td>
<td>S=Additional lithium carbonate, 0.43mmol/L (n=25) C= Placebo. (n=24)</td>
<td>MADRS, MMSE</td>
</tr>
<tr>
<td>Dinan, 1993 [46]</td>
<td>Observation al dose-response study, 1 week.</td>
<td>11 patients with depression, unresponsive to Sertraline for &gt;6 weeks.</td>
<td>S1=Sertraline +lithium carbonate, 0.6mEq/L (n=5) S2=Sertraline +lithium, 0.26mEq/L (n=6)</td>
<td>HRSD</td>
</tr>
<tr>
<td>Nagel et al, 1991 [29]</td>
<td>RCT double-blind pilot study, 2 weeks.</td>
<td>12 alcoholics in an abstinence phase (2 weeks after latest drink).</td>
<td>S= Lithium Carbonate, 0.3-0.5mEq/L (n=6) C= Placebo (=decavitamines)n=6)</td>
<td>MSRS</td>
</tr>
</tbody>
</table>

RCT= Randomized controlled trial. AD=Alzheimer’s Disease. MMSE=Mini Mental State Examination test. aMCI=amnestic Mild Cognitive Impairment. CDR= The Clinical Dementia Rating scale. ADAS-cog= Cognitive Subscale of the Alzheimer’s Disease Assessment Scale. CERAD= Consortium to Establish a Registry for Alzheimer’s Disease Delayed recall test. CSF=cerebrospinal fluids. CGI-S= Clinical Global Impression-Improvement Scale. MADRS= Montgomery-Åsberg Depression Rating Scale. HRSD= Hamilton Rating Scale for Depression. NPRU=Naval Psychological Research Unit Mood Scale questionnaire. MSRS= Manic State Ratings Scale.
Table 2. The results and quality assessment according to GRADE of the analyzed trials

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Results</th>
<th>Quality Assessment (low, average, high risk for bias)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nunes et al, 2013 [41]</td>
<td>Subjects treated with lithium showed no decreased performance in MMSE score. Control group decreased in their performance on MMSE, significant difference.</td>
<td>A1=L A2=L A3=L A4=A A5=L A6=H Total=A</td>
</tr>
<tr>
<td>Forlenza et al, 2011 [42]</td>
<td>Lithium treated group had a better performance on the ADAS-cog and in attention tasks after 12 months and a significant decrease in the concentration of CSF biomarker P-tau, compared to the placebo group.</td>
<td>A1=L A2=L A3=L A4=L A5=L A6=A Total=L</td>
</tr>
<tr>
<td>Macdonald et al, 2008 [43]</td>
<td>Eight of 22 patients completed the trial. No difference between treated group and comparison group in MMSE or ADAS-cog score, before or after dropout.</td>
<td>A1=L A2=H A3=L A4=H A5=L A6=A Total=H</td>
</tr>
<tr>
<td>Alevizos et al, 2012 [44]</td>
<td>Mean CGI-S score decreased from 5.91 to 3.49 in 6 weeks. 51% of the patients were “much” or “very much” improved according to the CGI-S.</td>
<td>A1=H A2=H A3=H A4=A A5=L A6=L Total=H</td>
</tr>
<tr>
<td>Wilkinson et al, 2002 [45]</td>
<td>No significant difference between exposed group and placebo group regarding MADRS or MMSE. Significant difference in depression relapse rate over two years, eight in placebo vs one in exposed group.</td>
<td>A1=L A2=A A3=L A4=A A5=A A6=A Total=A</td>
</tr>
<tr>
<td>Dinan, 1993 [46]</td>
<td>Seven of the 11 patients were significantly improved after 1 week, mean HRSD dropped from 20.5 to 12.1. Two of the four non-improved were non-compliant. No difference in improvement between the groups.</td>
<td>A1=L A2=L A3=H A4=L A5=A A6=L Total=H</td>
</tr>
<tr>
<td>Schrauzer et al, 1994 [30]</td>
<td>Significant difference between lithium group and placebo group in NPRU results after 4 weeks, with a steady increase in the mood test score in the lithium group.</td>
<td>A1=L A2=L A3=A A4=L A5=L A6=L Total=L</td>
</tr>
<tr>
<td>Nagel et al, 1991 [29]</td>
<td>Significant drop in MSRS score for the lithium group during the 2-week period, nonsignificant change in ratings in the placebo group.</td>
<td>A1=H A2=L A3=A A4=L A5=L A6=L Total=A</td>
</tr>
</tbody>
</table>

MMSE=Mini Mental State Examination test. ADAS-cog=Cognitive Subscale of the Alzheimer’s Disease Assessment Scale. CSF=Cerebrospinal fluids, P-tau=phosphorylated Tau-protein. CGI-S=Clinical Global Impression-Improvement Scale. MADRS=Montgomery-Åsberg Depression Rating Scale. HRSD=Hamilton Rating Scale for Depression. NPRU=Naval Psychological Research Unit Mood Scale questionnaire. MSRS=Manic State Ratings Scale. A1=Selection bias, A2=Performance bias, A3=Detection bias, A4=Attrition, A5=Reporting bias, A6=Other considerations. L=Low risk for bias, A=Average risk for bias, H=High risk for bias.
Two of the three articles regarding dementia or aMCI found a positive result with lithium treatment on their patients. One had an average risk for bias, one a low risk for bias, and both were RCT (Table 1,2). Nunes et al got an average risk for bias, mainly due to an unexplained attrition rate of nearly 20% in both groups, and a probable conflict of economic interests [41]. Forlenza et al got a low risk for bias. The only issue was a possible conflict of interests with a comprehensive private donor list without mentioning conflict of interests [42]. Macdonald et al found no difference compared to placebo, was an open label study, and had a high risk for bias due to completely different terms between the groups, an attrition rate of 64%, and a possible conflict of interests (Table 1,2) [43].

All three articles about depression had positive results with lithium augmentation. Alevizos et al and Dinan had significant drops in the depression scale scores and were observational studies, and Wilkinson et al had a significant drop in depression relapse compared to placebo, and was RCT (table 1,2) [44–46]. Alevizos et al had a high risk for bias due to high selection bias without placebo/control and performance bias with allowed antipsychotic medication for an unknown number of patients. Wilkinson et al had an average risk for bias due to an attrition rate of 60.5%, a poorly report on what antidepressants the subjects took and partly being financed by Lorex Pharmaceuticals, NY, USA. Dinan had an average risk for bias due to a high performance bias with daily controls/conversional therapy for all patients during the study and a detection bias, due to the lack of a placebo control (table 1,2).

The two articles about mood in former addicts with microdose lithium treatment had positive results, and both were RCT. Schrauzer et al had a low risk for bias, and Nagel et al had an average risk for bias due to detection bias with a mood scale originally composed for patients with sleep deprivation and not alcoholics, and a possible inadequate placebo composed of decavitamines (Table 1,2) [29,30].

**Discussion**

The purpose of this review was to examine what evidence lithium treatment has in mental illness, other than bipolar disorder in a manic phase, in doses that generally are considered sub-therapeutic, and which conclusions that can be drawn from those data.

The results of Nunes et al and Forlenza et al’s were positive regarding lithium treatment, with no decline in MMSE or ADAS-cog compared to a decline in the placebo groups. These articles provide encouraging data on low dose lithium in the treatment of dementia, although further studies are needed. Macdonald et al had no significant results, and had a high risk for
bias (table 1,2). Further support for the results in dementia has recently been published, showing that even the small amounts of lithium available from drinking water have a protective affect against dementia [47,48].

Nunes et al’s weakness was that the study is the subject of a patent application regarding possible treatment for AD, which is a probable conflict of interests. A case can be made that the application did not affect the outcome of the study, and that the risk for bias therefore should be considered low and not high. Consequently, giving the result higher impact. A strength in Forlenza et al trial was that it showed that patients treated with lithium had a significant decrease in concentrations of CSF P-tau, an important hallmark for AD [14]. This gives interesting implications for further research. Macdonald et al was an observational open label study and with an attrition rate of 64%, which is considered unacceptably high. Also, the study was not placebo controlled, with comparison measurements from a cohort register. That gave a high probability of performance bias. Therefore, to draw conclusions from this study is problematic and results must be interpreted carefully.

All tree articles regarding depression were lithium augmentation studies with positive result with lithium augmentation (Table2). Alevizos main quality issue, apart from being observational, was that the selection was of a patient group which did not respond to Venlafaxine, an SNRI commonly not the first drug of choice in depression. This gives a very specific patient group which is hard to extract clinical implications from. And without placebo control it is not unlikely that the recovery followed a natural course, rather than being the result of lithium augmentation. Wilkinson et al was a RCT, but with a 60% attrition rate which impacts the quality assessment. It was also not reported what antidepressants the subjects took in relation to the reported side effects and drop out, which affects the ability to draw conclusions of the trial. Dinan was a dose-response study without placebo control, with half of the study population on lithium augmentation below 0.5mmol/L. The main problem with the trial was that it just underwent one week of exposure. In that time, every subject had daily interaction with clinicians, observing and analyzing HRSD results. This gives a high risk of confounding factors, that not only lithium was augmented, but also conversational therapy, daily routines etc. The only probable conclusion to extract is that the lithium concentration did not matter, and <0.5mmol/L was as efficient in this particular case.

Except from dementia and depression, the only other articles found were the two articles about alcoholics and former drug abusers. Both articles were double-blinded RCTs with positive results. Schrauzer et al had a low risk for bias, and Nagel et al an average risk (table
1,2). Schrauzer et al is widely quoted for being one of the first trials to show that microdoses of lithium has a clinical effect on patients, also being a well conducted study. And for example, Nunes et al references to that trial, which was one of the inspirations for their trial [41].

One possible weakness of the Schrauzer et al trial is the choice of mood scale. NPRU is not common in clinical practice and generally focuses on symptoms of sleep deprivation, thus making it difficult to draw clinical implications from the study [39]. Also, the clientele of former drug abusers in self-help programs, raises the question on confounders regarding mental and somatic health in general, that is not answered in the study. Though being a pilot study it is well conducted, and opens up new fields of study with microdose lithium treatment. Nagel et al conducted a trial with alcoholics starting the third week in a detoxification program. The patients had problems with sleep, hyperactivity and general irritability, which all are common problems in addiction and detoxification. Though being RCT, the randomization process is not described, and there was a possible baseline group difference regarding score on MSRS. Also, there was a possible detection bias with the Manic State Ratings Scale, MSRS. The scale was originally designed to assess symptoms of mania, and not specific for mood assessment in general. It is possible that other mood questionnaire would have been a better choice for the mood rating. Nagel et al’s choice of placebo, decavitamines, may have been a possible confounder. Decavitamines is a composition of vitamins, e.g. thiamine. This may have helped the placebo group’s mental state, given the fact that they were active alcoholics with a possible vitamin deficiency. However, if this confounder is relevant for the outcome should decrease the difference between the groups. Apart from that, Nagel et al gives clinical implications for new interesting ways of treating substance abusers in detoxification programs, with relative low risk of side effects.

In view of the favorable results on irritability, microdose lithium would be interesting to test as a treatment in patients with pre-menstrual dysphoric disorder (PMDD), a patient group who have both affective and behavioral changes, and not always are helped by the available treatments [49].

There was a difference in results in the literature search between using the words “low dose” or “low dosage”, with different results in both cases. That shows a possible weakness in the search process, and that important articles may have gone unnoticed. Though the included articles did not differ from known reviews in the area, apart from one included article (Dinan, 1993), which was found after screening references. The supervisor, an expert in the field, did
not find any more articles to include. Hence, there was only a small possibility that interesting articles was missed. When grading and assessing the quality of articles it is advised to use two separate assessors. In this case only the author graded and assessed the articles, making it possible it was bias. It should be noted that the supervisor was informed about the results and consolidated the findings, decreasing the possibility of grading bias. A strength with the review is that it found various articles from 1991 to 2013, giving a wide span and a solid base for future research.

For future research, the review’s result gave two implications:

1. All the studies are on relative small populations, where it is easier to find a difference between subject and control, but harder to get significant difference and more solid conclusions. For the future, it would benefit to conduct RCT on larger populations.
2. All studies had different study times and outcome measures, making a meta-analysis impossible to conduct. In order to get conclusions that have a higher clinical impact value, a more standardized approach should be used.

The results of the review gave two clinical implications:

1. Lithium in concentrations <0.5mmol/L could be an alternative in patients with mental illness when side effects from usually recommended dosage are less acceptable.
2. Lithium in microdoses could be an experimental treatment for patients with cognitive impairment or irritability, stabilizing their cognitive function and/or quality of life.

Conclusion

There is evidence supporting that lithium in doses <0.5mmol/L, and in microdoses could be used in clinical practice more frequently, e.g. in patients with irritability. Lithium in microdoses or serum concentrations <0.5mmol/L is a potentially beneficial treatment for patients with aMCI or dementia, and gives a positive outcome on cognitive functions. Lithium augmentation in concentrations <0.5mmol/L is a viable alternative in patients with refractory major depression. Further research is necessary to consolidate these findings.

Acknowledgements

I would like to thank my supervisor, Dr. Mats B. Humble. Dr. Humble’s deep and historic knowledge of lithium treatment is somewhat unparalleled in Sweden, and it would have been impossible to conduct this review without his insight.
I would also like to thank the librarian Linda Bejerstrand at The Medical Library, Campus USÖ, Örebro University. Her quick help locating obscure articles from the 80’s, and insightful support during my PubMed searches was of great importance.
References


Cover letter

Dear editor

Please consider the enclosed manuscript entitled “Low dose lithium treatment in patients with mental illness” for publication in your magazine.

We believe that this MS will be of particular interest to the readers for the following reasons:

- To our knowledge this is the first review to analyse clinical trials with low dose lithium treatment under concentrations of 0.5 mmol/L, and microdoses in dementia, depression, and mood disorders in addicts all together.
- The results shed new light to the power and diversity of lithium treatment, and will possibly give doctors a new tool to use when other drugs become inadequate, or when side effects from usual lithium dosage are regarded less acceptable.
- This review will consolidate the notion that lithium still is an underused drug with bigger potential then generally thought before, and may have a bigger therapeutic span.
- The conclusion of the review opens doors to new fields of study, and gives future clinical trials better background information that may sharpen their aim regarding dementia, depression and irritability.

The review is not being considered for publication elsewhere.

All authors have approved the final version of the manuscript and have no conflict of interest regarding this paper.

Best regards,

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Populärvetenskaplig sammanfattning


Djurstudier har visat att litium kan skydda nervceller från demens, och att litium antagligen hämmar GSK-3α, som annars är ett överaktivt och skadligt enzym vid Alzheimers demens. Idag är litium förstahandsbehandlingen vid bipolär sjukdom, och välanvänt vid depression. Man har nyligen sett att litiumbehandlade bipolära patienter i lägre utsträckning får demens.

I klinisk vardag sänker man ibland litiumdosen för att minska biverkningarna, ofta med någorlunda bevarad effekt. Dock är evidensläget något fattigt på material, och några större litteraturgenomgångar som bara kollar på lågdosbehandling har nog inte gjorts tidigare.


Vår förhoppning är att man i framtiden ännu bättre kan förstå litiumets diversifierade användningsområden, och eventuellt även identifiera ett botemedel mot demens.
**Etiskt övervägande**

Då detta är ett smalt område skulle det kunna hända (som undantag) att intressanta artiklar av typen pilotstudie inkluderades utan etiskt godkännande. I sådant fall krävs reflektion kring nytan av att ta med studien, med etiken i fokus. Då detta primärt är ett studentarbete och ej publiceringsstudie kan det finnas etiskt utrymme för att inkludera artiklar utan etiskt godkännande.


Vid publicering och formulering av min studie är det viktig att reflektera, så svårt sjuka patienter eventuellt inte får felaktig bild av resultatet, och till exempel vägrar normala doser litium. Detta ger negativa konsekvenser för patienten, dess anhöriga och involverad sjukhuspersonal. Det kan i värsta fall ge dödlig utgång. Det är därför viktigt att reflektera hur man betonar sina slutsatser och resultat, och därigenom minska risken för framtida missförstånd.

Det är lätt att låta sig påverkas av sitt forskningsområde, där man har ett brinnande intresse. Hur vet man att man inte har låtit förhoppningen om sina resultat påverka ens faktiska resultat. Det är viktigt att ha sin egen risk för bias i åtanke, och även resonera/bli granskad kring sin analys av en utomstående forskare.

Med ovan reflektion i åtanke är slutsatsen att det alltid måste göras ordentliga etiska analyser och reflektioner, även i skapande och publicerande av systematiska litteraturstudier.