Identifying the neuropsychiatric health effects of low-dose lithium interventions: A systematic review

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ABSTRACT

Background: Lithium is widely evidenced for its neuropsychiatric benefits. Advantages of ‘sub-therapeutic’ doses are increasingly being reported, which is apposite given enduring concerns around adverse effects of ‘therapeutic’ doses. We aimed to synthesise all available evidence from interventional studies investigating low-dose lithium (LDL) across neuropsychiatric outcomes.

Method: Electronic databases were systematically searched to include studies where a group of adult humans were treated with LDL (serum level ≤0.6 mmol/L), where data describing a neuropsychiatric outcome were reported either before and after treatment, and/or between lithium and a comparator.

Results: 18 articles were examined and grouped according to outcome domain (cognition, depression, mania, and related constructs e.g., suicidality). Significant benefits (versus placebo) were identified for attenuating cognitive decline, and potentially as an adjunctive therapy for people with depression/mania. Across studies, LDL was reported to be safe.

Conclusions: Despite the paucity and heterogeneity of studies, LDL’s apparent pro-cognitive effects and positive safety profile open promising avenues in the fields of neurodegeneration, and augmentation in affective disorders. We urge future examinations of LDL’s potential to prevent cognitive/affective syndromes.

1. Background

Disability associated with neuropsychiatric illness contributes more to the global burden of disease than any other single medical discipline (~28%) and may even be under-estimated due to compounding interactions between mental and physical health (e.g. poorer physical health outcomes for those with mental comorbidities and vice versa) (Prince et al., 2007). Notable here are reports of depressive disorders being the second leading cause of years lived with disability worldwide (Lancet Psychiatry, 2022) and of the rising prevalence of neuropsychiatric disorders (Bebbington and McManus, 2020; GBD, 2016) as well as exacerbations of common mental illnesses during the COVID-19 pandemic (COVID-19 Mental Disorders Collaborators, 2021).

For mood disorders, extensive evidence suggests that duration of untreated affective illness precedes poorer long-term outcomes and that subclinical symptoms are risk factors for future major episodes (Altamura et al., 2010; Drancourt et al., 2013). Indeed, the course of illness is typically prolonged further by, for example, high rates of untreated major depressive disorder (MDD) (Shah et al., 2021; Strawbridge et al., 2022) and long delays to accurate diagnosis (and therefore treatment) of bipolar disorder (Hirschfeld et al., 2003). For people with dementia, current treatments are not effectively halting illness progression, and pharmacological prescriptions require safety and metabolism considerations (The Lancet, 2020).

In general, many people express a preference for ‘natural’ substances than so-called synthetic medications (Scott et al., 2020), particularly for mental health conditions where access to non-pharmacological treatments is also challenging for many (Strawbridge et al., 2022). These latter scenarios may be particularly pertinent for individuals with mild or subclinical symptoms that, if ameliorated early, may prevent more severe affective illness. However, natural remedies and lifestyle interventions (e.g., dietary changes) have evidence bases that are limited in terms of quantity (number and size of trials), risk of bias, and/or small effect sizes (Yetley, 2007). Treatments that are acceptable to patients,
both in terms of initial acceptability and tolerability of side effects, and effective at symptom amelioration and/or prognosis improvement, are clearly needed transdiagnostically.

Lithium is the mainstay treatment for mood episodes in the context of bipolar disorder (Cousins et al., 2020), and not only has a robust evidence base for other mood disorders (Strawbridge et al., 2019; Young, 2017) but also reasonable evidence for its anti-suicide properties (Lewitza et al., 2015) (which may be independent of its mood stabilising effect (Song et al., 2017)). Clinically therapeutic doses of lithium (as delineated in treatment guidelines) are associated with adverse effects such as renal and thyroid dysfunction (Strawbridge and Young, 2022), which can be mitigated or addressed through regular monitoring of blood monitoring. However, it is a concern for the vulnerable elderly when considering lithium as a putative treatment for people with Alzheimer’s dementia, an area which is gaining momentum (Matsunaga et al., 2015).

Several reports suggest that ‘sub-therapeutic’ doses confer significant benefits to affect (Post, 2018) and cognition (Mauer et al., 2014) with a reduced risk of side effects. Potentially, ‘sub-therapeutic’ even applies to the extent of trace elemental lithium, though perhaps only when consumed at extremely low ‘doses’ over a prolonged period. Lithium salts are naturally present in most rocks and as such trace levels are naturally apparent in mineral water, albeit at various concentrations dependent on location. Collating all of the internationally available data, a statistically significant association was recently derived between areas in the world with higher levels of trace lithium in tap water and reduced suicide rates (Memon and Rogers, 2020). This finding did not appear to be confounded by social or demographic factors, but while significant at a population level, the findings remain uncertain as to individual benefits. The potential benefits of trace lithium exposure are not confined to incidental ecological associations. There are now increasing calls for recommended dietary lithium intake (1 mg per day) and fortification in food on the basis that this putative ‘micronutrient’ has pleiotropic benefits not only to mood and the reduction of violence or aggression but also in facilitating the functions of vitamins and folates (Schrauzer, 2002). Lithium consumed in the diet appears to be bioavailable, based on biochemical mechanistic theory, (Szkłarska and Rzymski, 2019) preclinical data, (Seidel et al., 2020) and preliminary pharmacokinetic data (Seidel et al., 2019). The bioavailability, potential benefits and safety profile of alternative lithium formulations, such as lithium orotate (which is not regulated and available from health food outlets), therefore, requires consideration and further investigation (Pacholko and Bekar, 2021; Murbach et al., 2021).

Due to the well-documented interplay between affective disorders, substance use disorders and neurodegenerative disorders (The Lancet, 2020) and the extant evidence for high-dose lithium benefitting each of these (Cousins et al., 2020; Strawbridge et al., 2019; Young, 2017; Lewitza et al., 2015; Matsunaga et al., 2015), a synthesis of the literature on low-dose lithium is warranted for its neuropsychiatric effects as a whole.

2. Objectives

This systematic review aimed to synthesise interventional studies (randomised or non-randomised) of low-dose lithium treatment for any human adult population assessing an outcome related to psychiatric or neurological health. Most reviews have focused on lithium carbonate, but as other forms are available, we chose to consider all formulations of lithium treatment. As a secondary objective, we aimed to synthesis findings across each outcome subgroup (e.g., affect, cognition). Both within-subject (before/after treatment) and between-subject (between lithium and any other treatment/control allocation) comparisons were planned, dependent on the available data, to ascertain whether low-dose lithium presents benefits or risks for neuropsychiatric health.

3. Materials and methods

3.1. Protocol and Registration

This review adheres to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2015). The review protocol was pre-registered to PROSPERO (the international prospective register of systematic reviews) (2021; CRD42021250306). The review methods align with those published in the protocol, with two exceptions as follows. First, we pre-specified the inclusion of all forms from approved medication (lithium carbonate or lithium citrate) to supplemental forms (e.g., lithium orotate), other than those known to be toxic in humans (e.g., lithium chloride). However, despite early concerns (Hainon et al., 1949) and the lack of current license, the authors reached a consensus that these concerns are not unanimous, and lithium chloride was considered eligible. Second, we revised the definition of low-dose after noting that studies differed widely in their reporting of target and actual lithium levels/doses. Initially, it was stated that eligible studies would need to have defined an upper dose of lithium equating to < 112.5 mg (equivalent to < 600 mg lithium carbonate) or an upper limit for serum lithium levels of 0.6 mmol/L. This was altered slightly as the review progressed as very few studies explicitly stated these restrictions on lithium dose, but many reported resultant (as opposed to target) lithium levels below that upper limit. Further, we permitted studies to be included where they reported a mean serum lithium level below the ‘lower therapeutic limit’ as conventionally considered in treatment guidelines for mood disorders (National Collaborating Centre for Mental Health, 2020) i.e., below 0.6 millimoles per litre (mmol/L).

3.2. Study eligibility criteria

Studies were eligible for inclusion if: (i) the study design was interventional; (ii) adult human participants were examined; (iii) an outcome related to psychiatric or neurological health was reported; (iv) at least some participants were allocated a low-dose lithium intervention (as defined above) with data reported on these. Pharmacokinetic studies were excluded due to the lack of expected neuropsychiatric benefits, but otherwise, no minimum duration of lithium treatment was specified. The nature of treatment comparators were not considered for study eligibility/exclusion, providing there were data available to enable an ‘untreated with lithium’ comparison i.e., a between-subject comparison (an untreated group to be compared with a treated group) or within-subject comparison (pre-treatment versus post-treatment measure of the outcome). No further exclusion criteria were planned, including language restrictions except when no adequate translation could be obtained.

3.3. Search strategy

PubMed/MEDLINE, Embase and PsycINFO were systematically searched to identify all eligible articles. All available dates were searched up to 11th June 2021. The following terms were used, searching within record titles, abstracts and keywords: ((lithium) AND ((low dose) OR (low-dose) OR (microdose) OR (micro-dose) OR (miniscule) OR (minute) OR (sub-therap*) OR (subtherap*) OR (sub-clinical) OR (sub-clinical))). Relevant reviews, notable articles, and the reference lists of included studies were also hand-searched.

Two reviewers (GG and GB, HF and HP, in pairs) independently assessed all retrieved records for inclusion using Rayyan open-source review management software (Ouzzani et al., 2016). Reviewers were aware of the review’s objectives but were blinded to the ratings of the other reviewers prior to final study inclusion. In the first stage, reviewers screened article titles and abstracts. In the second stage, the full texts of any potential articles were examined. Any discrepancies between reviewers’ ratings were consulted by a third reviewer (RS). Subsequently,
3.4. Data extraction

Two reviewers (of GG, GB, HF, HP, RS and JKG) independently extracted the following information from included studies using a standardised form: article information (including corresponding author contact detail, publication year, country/ies of study), methodological information (including information regarding participants, design, intervention and control conditions, outcome assessment and results data.) One reviewer (JKG) checked for discrepancies between the data extracted and consensus was achieved using the same methods as described above (consultation with RS, additional consensus with AHY and MJ). This approach was concurrently taken also for the risk of bias (RoB) assessment.

3.5. Risk of bias assessments

A standardised RoB assessment was undertaken for all included studies. As pre-specified, this comprised the Cochrane RoB tool (Higgins and Green, 2011) for randomised studies and the ROBINS tool (Sterne et al., 2016) for non-randomised studies, which were together modified slightly to maximise comparability between assessments for randomised and non-randomised investigations which were thus rated using the same criteria. The RoB domains considered were those arising from the randomization process (where applicable), blinding, treatment group comparability, outcome assessment, intention to treat analyses and deviation from pre-specified methods. Disagreements between RoB ratings were resolved as for other data extraction discrepancies. As recommended, an overall RoB ‘score’ was not planned (Cochrane).

3.6. Outcomes

It was anticipated that the majority of studies would assess ≥ 1 of the following outcomes (joint primary outcomes):
1) Affect; depressive symptoms or illness severity.
2) Affect; mania symptoms or illness severity.
3) Cognition; cognitive function, mild cognitive impairment (MCI) severity or conversion to dementia.
4) Suicidality; severity or frequency of e.g. self-harm events.

If multiple assessments were reported for any of the above outcomes within a study, first, validated instruments would be prioritised over non-validated measures and second, clinician-rated measures were to be prioritised over patient-rated assessments.

Additional (secondary) outcomes were planned to include constructs related to the above e.g. anxiety, sleep, agitation, substance use, and other neuropsychiatric illness severity outcomes.

3.7. Analysis

Comparisons were planned for assessments pertaining to the above constructs. Where possible, both within-subject (pre-lithium versus post-lithium assessments) and between-subject (lithium versus comparator intervention effects) were planned. For continuous outcome measures, we planned to use a standardised effect size (Cohen’s d or Hedges’ g) and for dichotomous outcomes, a relative risk/odds ratio. Where sufficient data from homogenous studies were available (>3 comparisons per outcome), a random effects within-subjects meta-analysis was planned, and (for methodology, see Scott et al., 2022); where not appropriate or not available, a systematic narrative synthesis was planned according to the Synthesis Without Meta-analysis (SWiM) approach (Campbell et al., 2020).

4. Results

4.1. Study selection

The results for including studies are presented in Fig. 1 (PRISMA flowchart). The systematic search generated 3400 records after duplicates were removed, including 46 identified through handsearching. After screening record titles and abstracts, 147 articles’ full texts were reviewed for eligibility. A total of 18 articles describing 16 studies were included.

4.2. Study characteristics

Baseline study characteristics for all included studies are presented in Table 1. Thirteen RCTs and three non-randomised single- or two-arm trials were included. Studies most often compared low-dose lithium to placebo (9 studies), while others compared low-dose lithium to treatment as usual (TAU; 3 studies), standard-dose lithium (4 studies) or another medication (1 study). Four studies used low-dose lithium as an augmentation or in combination with antidepressants; most studies added lithium to usual care, and three studies we report as examining lithium monotherapy. Of these lithium ‘monotherapy’ studies, pro re nata use of sedative medications was permitted in the study involving manic patients (Stokes et al., 1976) and one of the studies of euthymic BD patients, (Nolen and Weisler, 2013) while the other euthymic BD study reported the use of additional medication only when patients experienced a relapse (and the main outcome of interest for this review was relapse rate) (Keller et al., 1992).

Populations studied included: bipolar disorder (5 studies), unipolar depression (1 study), unipolar or bipolar early-stage treatment-resistant depression (tRD; defined as non-response to current antidepressant treatment; 3 studies), Alzheimer’s Disease (2 studies), former drug or alcohol use disorders (2 studies), ultra-high risk for psychosis (1 study), amnesic mild cognitive impairment (1 study), and multiple sclerosis (1 study). Mean study size was n = 118 (SD = 179, range 11–742).

Thirteen studies used lithium carbonate, with target dose ranges between 0.3 mg and 1200 mg and/or target serum levels between 0.2 and 0.8 mmol/L (NB serum levels were not targeted in the lowest dose study). Only two studies reported mean actual dose, ranging from 353 mg to 710 mg. Where reported, actual serum levels ranged from 0.26 mmol/L to 0.57 mmol/L. Three studies included formulations other than lithium carbonate: lithium chloride (Stokes et al., 1976); lithium carbonate or gluconate (Nunes et al., 2013); and ionic lithium (Schrauer and de Vroey, 1994). Reported treatment duration ranged from 1 (Dinan, 1993) to 104 (Nolen and Weisler, 2013; Forlenza et al., 2019) weeks, but the duration was not described in one study (Keller et al., 1992). Due to heterogeneity in trial design and outcome reporting across studies, a meta-analysis was not appropriate, therefore results are presented narratively.

4.3. Depression

Seven studies examined the effect of low-dose lithium on depression (Table 2). Two studies using lithium to augment current antidepressant treatment in those with unipolar or bipolar tRD reported improvements in depression symptoms after lithium treatment (Dinan, 1993; Alevizos et al., 2012). However, one augmentation trial for tRD (Stein and Bernard, 1993) reported no significant difference from placebo and a combination study (lithium with citalopram for people with unipolar depression) (Khan et al., 2011) also reported no significant differences from placebo. Further, in a study of people with bipolar disorder who were experiencing an episode of illness, non-significant differences in depression were reported comparing lithium combined with optimised TAU versus optimised TAU alone (Nierenberg et al., 2013). The only study of people with bipolar affective disorders not currently in an episode (after switch from quetiapine) also found no differences in
depression between lithium monotherapy and placebo (Nolen and Weisler, 2013; Nierenberg et al., 2013). Finally, a cross-over trial of individuals with multiple sclerosis reported significantly greater improvements in depression after lithium treatment compared to observation (Rinker et al., 2020).

4.4. Mania

Seven studies examined the effect of low-dose lithium on mania (Table 3). Three of these studies also included a standard-dose lithium comparison (Stokes et al., 1976; Nolen and Weisler, 2013; Keller et al., 1992). Low-dose lithium did not outperform placebo (Stokes et al., 1976), carbamazepine (Okuma et al., 1990), or TAU (Nierenberg et al., 2013) in reducing manic symptoms in patients with bipolar disorder experiencing a mixed/mania episode. Of the two studies of lithium monotherapy for euthymic patients, one identified no significant differences in mania compared to placebo, (Nolen and Weisler, 2013) whilst the other found that, similar to placebo, low-dose lithium was associated with a shorter time to recurrence of any mood episode compared to those taking standard-dose lithium (Nolen and Weisler, 2013; Keller et al., 1992). In a study of lithium monotherapy for patients experiencing mania, equivalent mania remission rates were reported between low-dose and standard-dose lithium (both 21%) (Stokes et al., 1976). However, low-dose lithium did not significantly improve manic symptoms in individuals with Alzheimer’s disease in comparison to placebo (Devanand et al., 2021), but one study in alcohol use disorder reported significantly greater improvements in manic symptoms in those treated with low-dose lithium compared to placebo (Nagel et al., 1991).

4.5. Cognition

Four studies examined the effect of low-dose lithium on cognition (Table 4). One study in Alzheimer’s disease reported significantly better performance on the Mini Mental State Exam (MMSE) in those treated with low-dose lithium compared to placebo (Nunes et al., 2013). In contrast, another reported no significance differences between groups (Devanand et al., 2021). A third (Forlenza et al., 2019; Forlenza et al., 2011) reported significantly less cognitive decline as well as improvements in functional performance and memory in individuals with amnestic mild cognitive impairment treated with low-dose lithium (after 12 and 24 months) compared to placebo. Finally, a cross-over trial in multiple sclerosis found no significant differences in tests of attention, working memory, and processing speed during low-dose lithium treatment compared to observation phases (Rinker et al., 2020).

4.6. Other outcomes

Seven studies reported additional neuropsychiatric outcomes: global impression in neurodegenerative illnesses (n = 2), fatigue in multiple sclerosis (n = 1), suicidality in unipolar or bipolar depression (n = 2), positive and negative symptoms in ultra-high risk for psychosis (n = 1), and general affect in former drug users (n = 1). In Alzheimer’s disease, 37% of patients receiving low-dose lithium were classified as responders based on clinical global impression (CGI) global change, compared to 0% of participants receiving placebo (Devanand et al., 2021). Total scores on the Neuropsychiatric Inventory (NPI) did not significantly differ between groups, however participants receiving lithium showed significantly greater improvements in delusion and irritability/lability subscales. In a study of patients with multiple sclerosis, no significant differences were identified for change in illness severity or fatigue during low-dose lithium treatment versus observation phases (Rinker et al., 2020).

No significant between-group differences were found in change in suicidality scores in patients with bipolar disorder treated with low-dose lithium compared to TAU (Nierenberg et al., 2013). Similarly, change in suicidality scores did not significantly differ in those with unipolar depression treated with citalopram plus low-dose lithium compared to placebo (Khan et al., 2011). However, suicidality remission rates in the lithium-treated group (30%) were double that of the placebo group (15%). Berger et al. (2012) found reductions in negative symptoms and overall psychotic symptoms in patients at risk of psychosis treated with low-dose lithium or TAU, but between-group significance testing was not reported. Finally, significant improvements in mood were in former drug users treated with low-dose lithium over four weeks (Schrauzer and...
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Table 1

Methodological characteristics of studies.

| Reference | Population | Trial design | Intervention | N | Duration (weeks) | Mean age (years) | % female | Target li dose/level | Mean actual li dose / level assessed |
|-----------|------------|--------------|--------------|---|------------------|------------------|---------|---------------------|-------------------------------------|
| Alevizos et al. (2012) | Uni/bipolar | RCT | Li aug | 51 | 5 | 44 | 64% | 300-450 mg | 353 mg / 0.33 mmol/L |
| Berger et al. (2012) | UHR psychosis | RCT | Li aug venlafaxine | 25 | 12 | NR | NR | 450 mg | 0.23 mmol/L |
| Devanand et al. (2021) | Alzheimer’s | RCT | Li aug | 38 | 12 | 76 / 74 | 23% | 150-600 mg | 0.2-0.6 mmol/L |
| Dinan (1993) | RCT | Li aug sertraline | 6 | 1 | NR | 67% | 400 mg | 0.26 mmol/L |
| Forlenza et al. (2019), Forlenza et al. (2011) | Amnesic MCI | RCT | Li aug | 31 | 104 | 71 / 74 | 74% | 150-600 mg | 0.62-0.5 mmol/L |
| Keller et al. (1992), Gelenberg et al. (1989) | BD (euthymic) | RCT | Li aug | 47 | NR | 38 | 55% | 0.4-0.6 mmol/L | 0.57 mmol/L |
| Khan et al. (2011) | MDD, DYS, DEP-NOS | RCT | Li aug + citalopram | 40 | 4 | 45 | 39 | 48% | 300 mg | NR |
| Nierenberg et al. (2013) | BD-I, BD-II (episodic) | RCT | Li aug + OPT | 141 | 24 | 39 | 39 | 55% | 600 mg x 8w then adjusted | 0.47 mmol/L |
| Nolen & Weisler (2013) | BD-I (euthymic) | RCT | Li aug | 137 | 104 | 37 | 40 | 65% | 900 mg / 0.6 mmol/L | 0.33 mmol/L |
| Nunes et al. (2013) | Alzheimer’s | RCT | Li aug | 58 | 60 | 55 | 77 | 78 | 59% | 300 μg | NR |
| Okuma et al. (1990) | BD (manic/mixed) | RCT | Li aug | 54 | 4 | NR | 57% | 200-1200 mg | 710 mg / 0.46 mmol/L |
| Rinker et al. (2020) | Multiple sclerosis | RCT | Li aug | 23 | 52 | 51 | 39% | 150-300 mg | 0.5-0.8 mmol/L |
| Schrauzer & de Vroey (1993) | Former drug users | RCT | Li aug | 12 | 4 | 29 | 33% | 400 μg | NR |
| Stein & Bernadt (1993) | BD-I | RCT | Li aug | 16 | 3 | 47 | 47 | 75% | 250 mg | NR |
| Stokes et al. (1976) | BD (manic) | RCT | Li aug | 38 | 20 | 45 | 49% | 0.24mEq/kg | 0.43 mmol/L |

Abbreviations: n = number of participants, tRD = early-stage treatment-resistant depression, NRCT = non-randomised trial, mg = milligrams, TAU = treatment as usual, NR = not reported, RCT = randomised controlled trial, PBO = placebo, Aug = augmented onto, MCI = mild cognitive impairment, mmol/L = millimoles per litre, BD = bipolar disorder, MDD = major depressive disorder, OPT = optimised treatment as usual, μg = micrograms, TCA = tricyclic antidepressant, mEq = milliequivalents, UHR = ultra-high risk, DYS = dysthymia, DEP-NOS = depression not otherwise specified, AUD = alcohol use disorder.

* Standard dose lithium group also included but not reported here.

b Double-blind phase. An additional 104 week open-label extension phase was reported where only one neuropsychological outcome was collected (conversion to dementia).

*3 studies not (only) assessing lithium: Stokes et al. (1976) lithium chloride; Nunes et al. (2013) lithium carbonate or gluconate; Schrauzer de Vroey (1994) enriched yeast with ionic lithium.

*4 Year 1: 11 participants randomised to Li, 12 to observation. Year 2: remaining participants then received other trial arm [11 Li, 6 observation]/ All drop-outs occurred during year 1.

*5 Figures given for whole sample only; in other multiple-arm trials, figures are reported first for a lithium group and secondly control group (separated using “/”).

*6 Placebo-controlled phase only; 3 weeks (after which dose increased in both groups; not eligible for this review.)

*7 Participants were randomised based on starting dose in two phases. Phase 1: randomised to alternating medium/placebo doses (medium-placebo-medium-placebo not eligible for this review.)

*8 All but three studies (Keller et al., 1992; Nunes et al., 2013; Berger et al., 2012) reported information on adverse events (AEs), severe adverse events (SAEs), or lithium toxicity. Low-dose lithium was not reported to be associated with a greater risk of AEs or SAEs compared to placebo (Nolen and Weisler, 2013; Schrauzer and de Vroey, 1994; Forlenza et al., 2019; Stein and Bernadt, 1993; Khan et al., 2011; Devanand et al., 2021; Nagel et al., 1991; Forlenza et al., 2011), TAU (Nierenberg et al., 2013), or carbamazepine (Okuma et al., 1990). Two studies suggested better tolerability of low-dose compared to standard-dose lithium, with one reporting nausea rates of 60% (standard-dose) compared to 17% (low-dose), (Dinan, 1993) and another reporting lithium toxicity in 13% (medium/high dose) compared to 0% (low-dose/placebo) (Stokes et al., 1976). The other notable finding was that in the largest of the included studies, similar rates of AEs and SAEs were reported across patients treated with placebo, low-dose, or standard-dose lithium (Nolen and Weisler, 2013).

4.7 Adverse events

All but three studies (Keller et al., 1992; Nunes et al., 2013; Berger et al., 2012) reported information on adverse events (AEs), severe adverse events (SAEs), or lithium toxicity. Low-dose lithium was not reported to be associated with a greater risk of AEs or SAEs compared to placebo (Nolen and Weisler, 2013; Schrauzer and de Vroey, 1994; Forlenza et al., 2019; Stein and Bernadt, 1993; Khan et al., 2011; Devanand et al., 2021; Nagel et al., 1991; Forlenza et al., 2011), TAU (Nierenberg et al., 2013), or carbamazepine (Okuma et al., 1990). Two studies suggested better tolerability of low-dose compared to standard-dose lithium, with one reporting nausea rates of 60% (standard-dose) compared to 17% (low-dose), (Dinan, 1993) and another reporting lithium toxicity in 13% (medium/high dose) compared to 0% (low-dose/placebo) (Stokes et al., 1976). The other notable finding was that in the largest of the included studies, similar rates of AEs and SAEs were reported across patients treated with placebo, low-dose, or standard-dose lithium (Nolen and Weisler, 2013).

4.8 Risk of bias assessment

See Supplementary table S1. Five studies were considered low RoB, five moderate, and six high RoB. Thus, 38% of studies were judged to have a high RoB. Studies often did not report details of randomisation procedures or pre-register study protocols, resulting in unclear RoB ratings. Most studies were rated low RoB in relation to equal treatment of groups and blinding of group allocation.

Fig. 2 presents a summary of studies’ findings categorised by how positive their results were, and displaying study-specific factors which...
may contribute to the heterogeneity of findings.

5. Discussion

Lithium is best evidenced for its mood stabilisation effects for people with bipolar and unipolar mood disorders, but its anti-suicide effects are well recognised and there is mounting interest in its pro-cognitive effects, which may expand the scope of interventions from affective disorders to other areas of neuropsychiatric health. It is unclear whether the ‘therapeutic reference range’ established for affective disorder is applicable to the other putative indications, or indeed whether lower doses for those with affective disorders might be considered preferable. It is unclear whether the therapeutic reference range established for affective disorder is applicable to the other putative indications, or indeed whether lower doses for those with affective disorders might be considered preferable. It is unclear whether the therapeutic reference range established for affective disorder is applicable to the other putative indications, or indeed whether lower doses for those with affective disorders might be considered preferable.

For mania, the rate of positive studies was the same as for depression (3/7). When limiting the comparison to the two studies which assessed mania outcomes in bipolar disorder patients experiencing a manic (or mixed) episode, both reported significantly (Okuma et al., 2012) positive findings, although both were at a high risk of bias. For cognition, 3/4 studies were positive, rising to 3/3 when limiting to participants with a specific outcome at baseline (e.g., multiple sclerosis (Rinker et al., 2020) or somewhat (Stokes et al., 1976) positive findings, although both were at a high risk of bias. For cognition, 3/4 studies were positive, rising to 3/3 when limiting to participants with a specific outcome at baseline (e.g., multiple sclerosis (Rinker et al., 2020) or somewhat (Stokes et al., 1976) positive findings).

Overall, considering all outcomes, approximately half of the included studies appeared to show positive effects for low-dose lithium. Of these, most studies had weaknesses in areas such as design (most notably, only having one treatment arm (Alevizos et al., 2012)), recruiting populations who were not in an episode mirroring the outcome at baseline (e.g., multiple sclerosis (Rinker et al., 2020) or non-active substance use disorders (Schrauzer and de Vroey, 1994; Nagel et al., 1991)), small numbers of participants (Schrauzer and de Vroey, 1994; Dinan, 1993; Nagel et al., 1991), short durations of lithium treatment (Dinan, 1993; Nagel et al., 1991), extremely low doses (Nunes et al., 2012; Schrauzer and de Vroey, 1994) and/or a high risk of bias (Schrauzer and de Vroey, 1994; Dinan, 1993; Nagel et al., 1991). Only one of the eight positive studies did not suffer any of these concerns – a long-term trial of lithium carbonate for amnestic MCI (Forlenza et al., 2019; Forlenza et al., 2011). A further three trials showed some positive effects (for mania, cognition, and

### Table 2

| Study                              | Population               | Continuation treatment | Duration (weeks) | Target Li dose/level | N     | Outcome measure | Efficacy (continuous) | Efficacy (binary)   |
|------------------------------------|--------------------------|------------------------|------------------|----------------------|-------|-----------------|-----------------------|---------------------|
| A. Within-subjects (pre-post lithium comparisons) | Uni/bipolar<br>tRD | Venlafaxine | 5 | 300-450 mg | 47 | CGI | Pre: 5.9, Post: 3.3 | Improved (p < .001) | 51% response |
| Alevizos et al. (2012)             |                          |                        |                  |                      |       |                 |                       |                     |
| Dinan (1993)                      | tRD                      | Sertraline             | 1 | 400 mg      | 6  | HAM-D          | Pre: 20.0, Post: 10.0 | Improved (p NR)     | 67% remission        |
| B. Between-subjects (lithium vs comparator comparisons) | MDD, DYS, DEP-NOS | Citalopram<sup>a</sup> | 4 | 300 mg      | 40 | MADRS         | Post-liiiium: – 11.8<sup>b</sup> | NS                  | NR                  |
| Khan et al. (2011)                |                          |                        |                  |                      |       |                 |                       |                     |
| Nierenberg et al. (2013)          | BD-I, BD-II (in episode) | OPT<sup>c</sup>        | 24               | 600 mg x 8w then adjusted | 116 | MADRS         | Post-liiiium: – 8.2<sup>c</sup> | NS                  | NR                  |
| Nolen & Weisler (2013)            | BD-I (euthymic)          | Sedatives only         | 104              | 900 mg / < 0.6 mmol/L | 137 | MADRS         | Post-liiiium: NR     | NS                  | NR                  |
| Rinker et al. (2020)              | Multiple sclerosis       | Various-TAU            | 52               | 150-300 mg / 0.5-0.8 mmol/L | 17  | BDI           | Post-liiiium: 12.3  | Improved, lithium > observation (p = .016) | NR                  |
| Stein & Bernadt (1993)            | tRD                      | TCA                    | 3                | 250 mg      | 16 | MADRS / HAM-D  | Post-liiiium: 21.6 / 16.5 | NS                  | Response: 18% Li, 22% placebo |

Abbreviations: n = number of participants, tRD = early-stage treatment-resistant depression, mg = milligrams, CGI = , HAM-D = , NR = not reported, MDD = major depressive disorder, DEP-NOS = depression not otherwise specified, DYS = dysthymia, MADRS = , NS = not significant, BD = bipolar disorder, OPT = optimised treatment as usual, mmol/L = milimoles per litre, BDI = Beck Depression Inventory, TCA = tricyclic antidepressant, w = weeks, NS = non-significant.

<sup>a</sup> Estimated from figure.<br> <sup>b</sup> Combination; lithium and intervention listed here initiated concurrently.<br> <sup>c</sup> Mean change from baseline.
general psychiatric symptoms), and although 2/3 were at a high risk of bias (Stokes et al., 1976; Berger et al., 2012), fewer issues were evident compared to the more substantively positive studies noted above. Of the five 'not positive' studies (4 depression, 3 mania), none were at a high risk of bias, but two recruited euthymic participants (thereby reducing the therapeutic potential for these outcomes (Nolen and Weisler, 2013; Severus et al., 2008). It is also well understood that the clinical benefits of lithium, and the decision to continue treatment at standard doses, when depression augmentation reports are included (Dinan, 1993). In practice, the appropriate dose will be determined by an individual’s presenting symptoms, course of illness and concomitant treatments (Severus et al., 2008). It is also well understood that the clinical benefits of lithium, and the decision to continue treatment at standard doses, needs to be balanced against the potential harms such as renal impairment (Strawbridge and Young, 2022). However, the encouraging findings from some studies of low-dose lithium suggest that it may be a

### Table 3

| Study | Population | Continuation treatment | Duration (weeks) | Target Li dose/ level | N | Outcome measure | Efficacy (continuous) | Efficacy (binary) |
|-------|------------|------------------------|-----------------|----------------------|---|----------------|----------------------|------------------|
| A. Within-subjects (pre-post lithium) comparisons | | | | | | | | |
| Keller et al. (1992), Gelenberg et al. (1989) | BD (euthymic) AUD (detoxed) | Sedatives only | None | 0.4–0.6 mmol/L | 47 | PSR | Severity scores | Significance |
| Nagel et al. (1991) | | | 2 | 300 mg | 6 | MSRS | Pre: 16.0<sup>a</sup>, Post: 10.0<sup>a</sup> | Improved (p < .05) |
| Okuma et al. (1990) | BD ( manic/ mixed episode) | Various | 4 | 200–1200 mg | 51 | CPRG | Post-lithium: 39.2 | NR |
| B. Between-subjects (lithium vs comparator) comparisons | | | | | | | | |
| Devanand et al. (2021) | Alzheimer's disease | Various | 12 | 150–600 mg / 0.2–0.6 mmol/L | 38 | YMRS | Post-lithium: 3.1<sup>b</sup>, Post-placebo: 1.1<sup>b</sup> | Non-significant |
| Nagel et al. (1991) | AUD (detoxed) | None | 2 | 300 mg | 6 | MSRS | Post-lithium: 10.0<sup>b</sup>, Post-placebo: 15.0<sup>b</sup> | Improved, lithium vs placebo (p < .01) |
| Nierenberg et al. (2013) | BD type I/II (in episode) | OPT | 24 | 600 mg x 8w then adjusted | 116 | YMRS | Post-lithium + OPT: –6.4<sup>b</sup>, Post-OPT: –5.8<sup>b</sup>, Post-lithium + OPT: –1.22<sup>b</sup>, Post-OPT: –1.48<sup>b</sup> | Non-significant |
| Nolen & Weisler (2013) | BD type I (euthymic) | Sedatives only | 104 | 900 mg / < 0.6 mmol/L | 137 | YMRS | Post-lithium: NR, Post-placebo: NR | Non-significant |
| Okuma et al. (1990) | BD ( manic or mixed episode) | Various | 4 | 200–1200 mg | 51 | CPRG / FGIR | Post-lithium: 39.2 | Non-significant |
| Stokes et al. (1976) | BD ( manic) | Sedatives only | 20 days | 0.24mEq/kg | 38 | PWCG | Post-CBZ: 35.3 | Response |

### Abbreviations:

- n = number of participants, BD = bipolar disorder, NR = not reported, mmol/L = millimoles per litre, PSR = Psychiatric Status Ratings, mg = milligrams, MSRS = Manic State Rating Scale, CPRG = Clinical Psychopharmacology Research Group rating scale for mania, YMRS = Young Mania Rating Scale, OPT = optimised treatment as usual, w = weeks, CGI-BP = Clinical Global Impressions-Bipolar, FGIR = Final Global Improvement Rate, CBZ = carbamazepine, mEq = milliequivalents, PWCG = Payne Whitney Clinic Global scale, AUD = alcohol use disorder.
- c Both measures of global illness severity/improvement; neither measure improved significantly over time; continuous efficacy reported is for the CPRG and binary response measured using the FGIR.
- d Formulation other than lithium carbonate (chloride).

### References

- Stokes et al., 1976
- Berger et al., 2012
- Nolen and Weisler, 2013
- Severus et al., 2008
- Strawbridge and Young, 2022
Lithium might be engaged at low or even ultra-low doses, opening discussions as to the optimal strategy for the investigation of potential benefits in cognitive decline and dementia. Thus far, a wide range of doses have been used across a small number of trials and although a meta-analysis suggested benefits that do not appear to vary substantially by dose, (Matsunaga et al., 2015) a study which used doses comparable to those in bipolar disorder did not show positive effects and reported poor tolerability. The rationale for the use of low-dose lithium in prevention as well as treatment of cognitive impairment (Strawbridge and Young, 2022) is pertinent to other areas, such as those at risk of mood disorders and/or suicidality where other lines of evidence suggest that prolonged exposure to trace lithium decreases suicide as well as homi- 

disorders and/or suicidality where other lines of evidence suggest that 

Young, 2022) is pertinent to other areas, such as those at risk of mood disorders and/or suicidality where other lines of evidence suggest that prolonged exposure to trace lithium decreases suicide as well as homi-

There are also some emerging indications for which the therapeutic range of lithium is not established and where low doses may be a viable pharmacotherapeutic strategy, rationally conferring benefits compared to standard doses. It is plausible that the neuroprotective effects of lithium might be engaged at low or even ultra-low doses, opening discussion as to the optimal strategy for the investigation of potential benefits in cognitive decline and dementia. Thus far, a wide range of doses have been used across a small number of trials and although a

useful adjunct that is well tolerated, and the findings of this review may support individualised decisions regarding the choice of dose in those apparently benefitting at lower serum concentrations.

Table 4
Low-dose lithium effects on cognition (all between-subjects effects).

| Study                | Population       | Continuation treatment | Duration (weeks) | Target li dose/level | N | Outcome measure | Efficacy (continuous) | Efficacy (binary) |
|----------------------|------------------|------------------------|------------------|----------------------|---|-----------------|---------------------|-------------------|
| Devanand et al. (2021) | Alzheimer’s disease | Various                | 12               | 150–600 mg / 0.2–0.6 mmol/L | 38 | MMSE Post-lithium: 0.9<sup>a</sup> | Non-significant | NR |
| Forlenza et al. (2019, 2011) | Amnesic MCI | NR                  | 104              | 150–600 mg / 0.25–0.5 mmol/L | 31 | ADAS-Cog Post-lithium: 0.8<sup>c</sup> | Li less decline, p < .05 | Non-significant |
| Nunes et al. (2013)<sup>b</sup> | Alzheimer’s Disease | Various              | 60               | 300 μg               | 49 | MMSE Post-lithium: 19.8 | Li improvement, p < .05 | Conversion to dementia: 16% Li, 30% placebo |
| Rinker et al. (2013) | Multiple sclerosis | Various             | 52               | 150–300 mg / 0.5–0.8 mmol/L | 17 | PASAT Post-lithium: 2.1<sup>c</sup> | Non-significant | NR |

Abbreviations: n = number of participants, mg = milligrams, mmol/L = millimoles per litre, MMSE = Mini-Mental State Examination, NR = not reported, SIB = Severe Impairment Battery, MCI = mild cognitive impairment, ADAS-cog = Alzheimer’s Disease Assessment Scale, CDR-SoB = Clinical Dementia Rating sum of boxes, CERAD = Consortium to Establish a Registry for Alzheimer’s Disease, WAIS-III SLN = Wechsler Adult Intelligence Scale-III Sequence of Letters and Numbers, TMT= Trail Making Test, μg = microgram, PASAT = paced auditory serial addition test, SDMT = symbol digit modalit test.

In multiple-arm trials, N (analysed) is reported for the lithium group (top) and the comparator group (bottom).

<sup>a</sup> Mean change
<sup>b</sup> Collected at the end of an additional 104 week open-label extension phase.
<sup>c</sup> Formulation other than lithium carbonate (carbonate or gluconate)
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Moreover, even with its broad remit, our review has more common amongst studies with positive findings. Conversely, studies where participants were not symptomatic at baseline may reduce the intervention’s effect size, and this was more common in the less positive studies. Duration of treatment also varied widely, with some studies using relatively long intervention periods (up to two years) and others treating participants for only 1 or 2 weeks. This generates a level of complexity in interpreting the findings, especially for studies in bipolar disorder where the evidence for the prevention of episodes of depression is stronger than for acute episode treatment at standard doses. Likewise, the doses used in these studies ranged from less than 0.5 mg ionic lithium per day to over 100 mg.

Due to the small size and notable heterogeneity of the studies identified, it was considered inappropriate to undertake a quantitative meta-analysis. Our narrative synthesis was also challenged by this, especially the categorisation of studies into positive, potentially positive, and not positive. The ‘positive’ study category comprised those reporting a significant between- or within-subject effect, but several other studies did not report a quantitative between-subjects comparison. We further recognise that within-subject effects can be influenced by factors other than the study intervention. Our definition of ‘low-dose’ also requires consideration. Our original definition was more stringent than ultimately implemented, with the adjustment considered necessary because not all studies reported the actual target dose or upper limit, and some studies aiming for a high target dose yielded a lower serum level akin to that of specific low-dose studies. Permitting studies based on an achieved mean serum lithium level below 0.6 mmol/L meant that some participants in the studies included in this review are likely to have been prescribed a dose aimed at achieving standard therapeutic levels. For these not to be achieved at a ‘study level’ might indicate either that therapeutic effects manifested at lower doses, obviating the need to titrate further or that tolerability concerns in the study population precluded standard levels being reached. Ultimately, the concepts of high-dose, low-dose or standard therapeutic range may be replaced by condition-specific reference values.

The beneficial effects of low-dose lithium reported in some studies in this review should drive further research, particularly controlled interventions in well-powered studies conducted robustly (low risk of bias) for a dose and duration appropriate to the target population and outcome. From the evidence synthesised as well as other recent reviews, (Hsu et al., 2022) this is warranted across numerous outcomes from mania and depression to cognition and suicidality across diagnostic groups. Research across the lifespan is also justified, exploring for instance low-dose lithium in those at risk of developing psychiatric disorders or in the determination of optimal efficacy and tolerability in the vulnerable elderly (Devanand et al., 2021): Such endeavours will of course be underpinned by the vast knowledge of the pharmacokinetics and dynamics of lithium established over many decades of research, including the safety of long-term lithium treatment at appropriate doses.
Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2022.104975.

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