



Efficacy, effectiveness, and safety/tolerability of lithium in children and adolescents up to 18 years of age with conditions other than mood disorders: A scoping review

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ABSTRACT

In youth, lithium is an effective medication for mood disorders, particularly for mixed and manic episodes of bipolar disorder, and is generally well-tolerated. In some clinical contexts, lithium is used off-label to manage other conditions. We conducted a scoping review of studies on the efficacy/effectiveness and safety/tolerability of lithium for treating youths with psychiatric conditions other than mood disorders or neurological disorders. We searched EMBASE, MEDLINE, PsycINFO, PubMed, and ClinicalTrials.gov up to March 31, 2025, with no restrictions on language or document type. We included studies of any design involving children and adolescents (mean age up to 18) treated with lithium, either as monotherapy or in combination with other psychotropic agents. We assessed study quality using the appropriate NHLBI tools and visually summarized the results with a heat map displaying sample size by study design and conditions, as well as the timeline of included studies' publication years. From 2687 records initially identified, after de-duplication removal and screening, 367 full-text reports were assessed, and 41 studies were included in the review, grouped by type of psychiatric or neurological disorder, most of which had a small sample. Among the assessed studies, 60 % of were considered of "fair" quality and 40 % of "poor" quality. Overall, although the clinical use of lithium beyond bipolar disorder in youth is increasing, the underlying evidence base remains limited. More rigorous research based on RCTs and observational studies with designs aimed at reducing confounding are needed to guide clinical practice.

1. Introduction

Lithium is a monovalent cation with demonstrated efficacy/effectiveness in treating manic and depressive acute episodes as well as in preventing recurrence of bipolar disorder (BD) in adults and youths (Findling et al., 2015; Amerio et al., 2018; Duffy et al., 2018; Grant and

Salpekar, 2018; Pisano et al., 2019). Lithium is currently FDA approved from the age of 12 years for mixed and manic paediatric bipolar disorder, including the depressive and maintenance phases of the illness (Cortese et al., 2024).

In recent years, the proposed therapeutic window for the use of lithium in adults has been significantly expanded, with growing clinical

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experience supporting its use beyond mood disorders (Manchia et al., 2024). Converging evidence from preclinical and clinical models shows that lithium exerts regulatory effects on a wide range of brain pathways and targets that are crucial for neuroplasticity and neuroprotection, including neurotrophic factors, neurotransmitters, oxidative metabolism, apoptosis, neuronal structures and glia, second messenger systems, as well as biological systems such as the circadian rhythm and hypothalamic–pituitary–adrenal (HPA) axis (Bortolozzi et al., 2024; Pisano et al., 2019; Damri and Agam, 2024). Lithium can induce or modulate autophagy via Glycogen Synthase Kinase 3 beta (GSK3 β) inhibition affecting the mechanistic Target of Rapamycin/Adenosine Monophosphate activated protein kinase (mTOR/AMPK) axis, synaptogenesis, mitochondrial metabolism (Chatterjee and Beaulieu, 2022; Wang et al., 2024; Chatterjee and Beaulieu, 2022), and inositol depletion (mTOR-independent) (Sarkar et al., 2006).

Considering an example of a possible target beyond mood disorders, in anorexia nervosa (AN) – where prolonged fasting and hyperactivity promote pro-autophagic signalling – autophagy dysregulation has been proposed as a key mechanism linking energy adaptation with rigid control/selection behaviours (Pałasz et al., 2018; Kheloufi et al., 2014; Nobis et al., 2018; Van Niekerk et al., 2016). Recent studies have shown that excessive autophagy, initially protective, can lead to cellular damage and acute liver failure under conditions of severe caloric restriction (Pałasz et al., 2018; Kheloufi et al., 2014). For example, some studies reported acute liver injury in AN patients associated with severe dietary restriction, characterized by elevated transaminase levels and complete resolution after appropriate nutritional intervention (Pałasz et al., 2018; Kheloufi et al., 2014). Moreover, autophagy has been implicated in the neurobiology of AN, suggesting a role in neuronal plasticity and regulation of feeding behavior (Zhu et al., 2023). These findings support the hypothesis that autophagy may serve as a bridge between the physiological response to fasting and the expression of pathological behaviors in AN (Nobis et al., 2018; Van Niekerk et al., 2016). Lithium could potentially target these pathways. These findings suggest the possibility of investigating the potential benefits of lithium across a broad array of neuropsychiatric, neurological, and neurodegenerative disorders, as well as gastrointestinal diseases, cardiovascular diseases, and cancer, among other conditions.

Most data regarding the neuropsychiatric use of lithium in adults with conditions other than mood disorders concern its potential anti-suicidal, anti-aggressive, and neuroprotective effects. Beyond mood stabilization, evidence supports the lithium ability to reduce suicidal ideation and self-harming behaviors across psychiatric populations, effect that may also be linked to its ability to decrease impulsivity and aggression, two factors associated with suicidal behaviour (Sesso et al., 2024; Fernando et al., 2022). Notably, both victims and perpetrators of bullying are at significantly increased risk for non suicidal self injury (NSSI) and suicidal behaviors, both in the short- and long-term (Serafini et al., 2023). This association suggests that interventions such as lithium treatment, potentially targeting impulsivity and aggression, could potentially mitigate NSSI and suicidal risk in populations exposed to bullying (Serafini et al., 2023). Furthermore, evidence shows that modern antipsychotic agents including clozapine, olanzapine, quetiapine, ziprasidone, aripiprazole, and asenapine may contribute to reducing suicidal risk and other negative clinical outcomes particularly when combined with lithium; this combination appears to attenuate affective instability and psychotic features, which are themselves linked to suicidality (Pompili et al., 2016; Waszak et al., 2024; Tondo, 2025). In addition to its effects on mood and suicidality, lithium does not appear to impair cognitive performance and may even be associated with comparable or superior outcomes in domains such as working memory and verbal learning in patients with bipolar disorder (Burdick et al., 2020; Gitlin and Bauer, 2024). Translational studies further support the neuroprotective and neurotrophic properties of lithium, including inhibition of GSK-3 and increased levels of neurotrophic factors (Chatterjee and Beaulieu, 2022). Long-term exposure in adults has

been linked to a reduced risk of cognitive decline and dementia, even at low doses (Chen et al., 2022; Puglisi-Allegra et al., 2021; Shen et al., 2024). Beyond psychiatric disorders, lithium has been proposed for epilepsy, which is of particular importance because a significant proportion of epileptic patients suffer from psychiatric comorbidities such as anxiety, depression, postictal mania, psychosis, and other mood disorders, many of which might be responsive to lithium treatment (Bojja et al., 2022; Fisher et al., 2022).

Research on the use of lithium in children and adolescents for indications other than mood disorders is more limited (Pisano et al., 2019). However, in some clinical contexts and with variability across geographic regions and countries, lithium is used for youth with aggressive behaviors, including explosive aggression and conduct disorder (Pisano et al., 2019). It is also used, in monotherapy or in combination with other psychotropic drugs, to manage emotion dysregulation, impulsivity and aggressive behaviors in children and adolescents with a wide range of conditions such as substance abuse, suicidal behaviour, or gaming disorder (Janiri et al., 2024; Masi et al., 2009; Sesso et al., 2024). Such off-label use of lithium in youth populations has seen a gradual increase in recent years, possibly reflecting the growing clinical complexity of mood and behavioral disorders in children and adolescents (Gigliotti et al., 2025; Janiri et al., 2023; Uran and Akçay, 2024). Epidemiological data on pediatric psychopharmacology highlight a marked rise in psychotropic prescribing trends. A review published in 2023 providing an up-to-date summary of the extent of off-label use in pediatric patients showed that the proportion of off-label prescriptions could reach 94 % in clinical settings (Petkova et al., 2023). In Italy, for instance, the Italian Medicine Agency (AIFA) report documented an increase in the use of mood stabilizers in minors, though with notable regional variability (AIFA, 2024).

This trend raises potential clinical concerns regarding safety, especially in a population characterized by increased neurological vulnerability and continuous and rapid brain development that may be affected by lithium differently than adults (Amerio et al., 2018; Poels et al., 2025). Indeed, although lithium is generally well tolerated, it requires careful serum monitoring because even in children and adolescents, side effects can occur during treatment and may involve multiple systems, particularly the central nervous system, renal, endocrine (including thyroid), gastrointestinal, and dermatological systems (Grant and Salpekar, 2018). Side effects may be more pronounced in children and youth (National Institute for Health and Care Excellence (NICE), 2014; McClellan et al., 2007). In a 12-month retrospective cohort (n = 143), approximately 29 % developed elevated TSH, with about 15 % requiring thyroid replacement therapy (Güneş et al., 2022); renal function values usually remained within the normal range in the short term, although long term data from adults indicate an increased risk of chronic kidney disease with treatment duration; polyuria, polydipsia, and enuresis may be particularly challenging in pediatric populations, while weight gain and tremor are among the most common adverse effects (Gitlin et al., 2023). International guidelines (American Academy of Child and Adolescent Psychiatry (AACAP), 2018; National Institute for Health and Care Excellence, 2022, NICE NG222, 2022) recommend baseline and ongoing monitoring of renal function, thyroid function, electrolytes, and serum lithium levels to ensure safety. Specifically, baseline tests should include serum creatinine, blood urea nitrogen, electrolytes, TSH, and a pregnancy test in post-pubertal females, followed by regular monitoring of lithium levels, renal and thyroid function at intervals guided by age and clinical stability.

Considering all the possible benefits as well as the potential risks of lithium use in youth, to inform clinical psychopharmacological practice with children and adolescents specific evidence in this clinical population is needed, rather than simply extrapolating findings from adults (Janiri et al., 2023). The objective of this scoping review was to map the available evidence on the use of lithium, including its clinical efficacy/effectiveness, safety, and tolerability, in psychiatric disorders, including mood disorders, and in neurological disorders in youth. The

rationale for conducting a scoping review rather than a systematic review was to comprehensively map the available evidence on lithium, given the expected heterogeneity of study designs, populations, and outcomes. The review addressed the following research questions:

1. Which psychiatric and neurological conditions have been treated with lithium in children and adolescents beyond bipolar and depressive disorders?
2. What clinical outcomes, including potential benefits such as reductions in aggression, impulsivity, and suicidality, have been reported?
3. What safety concerns and adverse events have been documented?
4. What methodological gaps remain, to guide future research?

2. Methods

2.1. Protocol

This scoping review was conducted based on a protocol publicly available on the Open Science Framework (OSF), enhancing transparency and allowing reproducibility of our methods (<https://osf.io/r23zv>). Of note, when we conducted a scoping search to plan the protocol of our review, it became clear that a meta-analysis was not feasible. This was confirmed when we retrieved the studies from our scoping review. As shown in [Table 1](#), there were not enough effect sizes from the same study design and in relation to the same disorder that could be meta-analytically pooled. We opted for a scoping review rather than a systematic review, with the aim to provide a broad exploratory mapping rather than a narrower, focused synthesis.

2.2. Search strategy

A systematic literature search was conducted up to 31 March 2025 in EMBASE, MEDLINE, PsycINFO, and PubMed, with no date, type of document, or language restrictions. The following syntax and search terms were used in PubMed: *lithium AND (child OR children OR childhood OR schoolchild OR schoolchildren OR kid OR kids OR teenager OR teenagers OR teens OR adolescent OR adolescents OR adolescence OR pre-adolescence OR pre-adolescent OR young OR youngster OR youth OR youths OR boy OR boys OR girl OR girls OR schoolboy OR schoolgirl OR pre-pubertal OR pre-puber OR prepubertal OR prepuber OR prepuberty OR pre-puberty OR pubertal OR puber OR puberal OR pre-pubescent OR prepubescent OR pubescent* OR underaged OR pediatric* OR paediatric* OR "six year old OR "seven year old" OR "eight year old" OR "nine year old" OR "ten year old" OR "eleven year old" OR "twelve year old" OR "thirteen year old" OR "fourteen year old" OR "fifteen year old" OR "sixteen year old" OR "seventeen year old" OR "eighteen year old" OR "6 year old" OR "7 year old" OR "8 year old" OR "9 year old" OR "10 year old" OR "11 year old" OR "12 year old" OR "13 year old" OR "14 year old" OR "15 year old" OR "16 year old" OR "17 year old" OR "18 year old "six years old" OR "seven years old" OR "eight years old" OR "nine years old" OR "ten years old" OR "eleven years old" OR "twelve years old" OR "thirteen years old" OR "fourteen years old" OR "fifteen years old" OR "sixteen years old" OR "seventeen years old" OR "eighteen years old" OR "2 years old" OR "3 years old" OR "4 years old" OR "5 years old" OR "6 years old" OR "7 years old" OR "8 years old" OR "9 years old" OR "10 years old" OR "11 years old" OR "12 years old" OR "13 years old" OR "14 years old" OR "15 years old" OR "16 years old" OR "17 years old" OR "18 years old")*). The search syntax and terms were adapted accordingly for use in the other electronic databases (see Supplementary File 1). These searches were supplemented by screening ClinicalTrials.gov for any additional eligible unpublished studies. Reference lists of relevant reviews and included studies were screened to identify any additional eligible articles

2.3. Eligibility criteria

We included studies, of any design, quantitatively or qualitatively

reporting on the efficacy/effectiveness and/or safety/tolerability of lithium either in monotherapy or in combination with other psychotropic drugs, for neuropsychiatric conditions other than bipolar and depressive disorders, consistent with DSM/ICD classifications (American Psychiatric Association, APA, 1994; World Health Organization, WHO, 2019) if reported in the original studies, in children and adolescents up to 18. Conditions such as severe mood dysregulation disorder and mixed states were considered within the bipolar spectrum, since in most of the included studies they were diagnosed or managed as clinical manifestations of pediatric bipolar disorder.

2.4. Data management

References were managed using EndNote, and duplicate records were removed prior to screening. To avoid double counting, we screened for duplicate publications by cross-checking author lists, and recruitment periods. In cases of overlap, we retained the most complete or recent report and extracted data only once. Two duplicate pairs are indicated in the summary tables (* and #). No further duplicates were detected after this procedure.

2.5. Study selection and data extraction

Identified potentially eligible references were independently screened by two authors in a two-step process: a first screening was performed based on titles and abstracts, and then full texts were retrieved for the second screening. At both stages, any disagreement was resolved by consensus or arbitration by a senior author. Studies were excluded if they did not meet the pre-specified inclusion criteria:

- The population included participants older than 18 years or did not include children/adolescents.
- The condition treated was bipolar disorder, depressive disorder, or a mixed/severe mood dysregulation state considered part of the bipolar spectrum.
- Lithium was not used as the primary intervention, or used in combination with unspecified treatments.
- The study article did not report relevant quantitative data or qualitative information on efficacy/effectiveness or safety/tolerability.
- The study was conducted on non-human subjects or in vitro models.
- The publication type was a commentary, editorial or review without original data.

2.6. Data charting process

Data related to the disorder(s) or condition(S) for which lithium was used, first author, year of publication, design, number of cases and controls included in the studies, age range of enrolled patients, type, duration and dosage of drug therapy prescribed, clinical efficacy/effectiveness and safety/tolerability of lithium were extracted independently in duplicate by two authors using a standardized form, supervised by a senior author; discrepancies were resolved by discussion or adjudication. After screening and selecting studies, key study characteristics were extracted and organized according to population, condition, study design, and outcomes. To facilitate the synthesis, we generated post hoc (i.e., not planned in our protocol) a heat map illustrating the distribution of studies across psychiatric and neurological conditions by study type and sample size, and a timeline showing the chronological evolution of lithium research in pediatric populations.

2.7. Quality appraisal

Quality assessment was conducted using the NHLBI Study Quality Assessment Tools (<https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools>), applying the instrument appropriate to each study design, except for individual case reports for which no tools

Table 1
Use of Lithium in psychiatric disorders in youth.

Disorder/ condition	First author, year	Design	N (genre)	Age	Type and duration of pharmacological therapy	Lithium serum level	Outcomes	Effect estimates/ Findings	Tolerability
ADHD	Greenhill, 1973	RCT (crossover)	9 (NR)	6–16 y	Lithium carbonate 900–1500 mg/day alternating dextroamphetamine sulfate 10–30 mg/day or placebo for 3 months	NR	Hyperactivity	25 % response vs placebo/amphetamine	NR
	Delong, 1987 (single longitudinal study)	Prospective	19 (NR)	5.3–15.3 y	Lithium for mean 4.6 y	NR	Uncontrolled behavior	No improvement	Worsening in 8
	Licamele, 1989	Case report	1 (M)	7 y	Lithium carbonate 600 mg/day	NR	Mood lability and conduct disturbances	Improvement	No major or clinically relevant side effects
ASD	Bandou, 2010	Retrospective	4 (NR)	5–18 y	PH 5–60 mg/day + lithium carbonate 950 + 164 mg/day	NR	CGI-S	No improvement	No major or clinically relevant side effects
	Campbell, 1972	Controlled study (crossover)	10 cases, 10 controls (8 M, 2 F)	3–6 y	Lithium carbonate 450–900 mg/day vs Chlorpromazine 9–45 mg/day	NR	Explosiveness, aggression, hyperactivity	No improvement	GI, endocrine, and renal symptom, irritability
	Delong, 1987 (single longitudinal study)	Prospective	21 (NR)	5.3–18 y	Lithium for mean 4.6 y	NR	Uncontrolled behavior	Improvement in 6 patients	Worsening in 7 patients
	Veenhuizen, 1992	Case report	1 (M)	16 y	Lithium carbonate 600 mg/day	NR	Exhibitionistic behavior	Improvement	No major or clinically relevant side effects
	Mintz, 2019	Retrospective	7 (NR)	15.4 y	Lithium	0.6 mmol/L	CGI-I	14/19 improved (73.7 %); ADHD comorbidity predicted response ($p = 0.038$, OR=12.2)	42.1 % side effects (fatigue, tremors)
	Di Vara, 2022	Case report	1 (M)	11 y	Lithium carbonate up to 600 mg/day + Risperidone 2 mg/day	NR	Irritability, aggression and social/verbal deficits	Improvement	No major or clinically relevant side effects
Catatonia	Winerdal, 2024	Case report	1 (F)	17 y	Lithium sulphate 126 mg/day + Lorazepam 28 mg/day + Memantine 10 mg/day for 6 weeks	NR	Catatonia	Improvement	No major or clinically relevant side effects
Conduct disorder	Platt, 1981 *	RCT	8 lithium, 10 placebo, 8 haloperidol (NR)	5.83–12.92 y	Lithium carbonate 500–2000 mg/day for 6 weeks	Mean 2.89 mmol/L	PMT, MFFT, SCWT	Mild worsening in PMT performance. No improvements on other cognitive tests	NR
	Platt, 1984 *	RCT	20 lithium, 20 controls (NR)	6–12 y	Lithium carbonate 500–2000 mg/day for 6 weeks	NR	Aggression	Improvement similar to haloperidol	Fewer cognitive side effects vs haloperidol
	Vetro, 1985	Case series	17 (NR)	3–12 y	Lithium carbonate 26 mg/kg/day	Mean 0.68 mmol/L	Aggression, social interaction deficits	Improvement	Renal, GI, neurotoxic side effects, ↑ weight
	Delong, 1987 (single longitudinal study)	Prospective	33 (NR)	5.3–17.4 y	Lithium for mean 4.6 y	NR	Uncontrolled behavior	Improvement in 5 patients	No major or clinically relevant side effects
	Carlson, 1992	Observational	11 (NR)	5–12 y	Lithium carbonate 600–1500 mg/day for 8 weeks	NR	Aggression, irritability, behavior dyscontrol	Improvement in some children	No major or clinically relevant side effects
	Rifkin, 1997	RCT	14 lithium, 12 controls (NR)	12–17 y	Lithium 0.60–1.25 mg/day for 2 weeks	Mean 0.79 mmol/L	Uncontrolled behavior	No improvement	Autonomic side effects

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Table 1 (continued)

Disorder/ condition	First author, year	Design	N (genre)	Age	Type and duration of pharmacological therapy	Lithium serum level	Outcomes	Effect estimates/ Findings	Tolerability
5 IDD	Malone, 1998 #	RCT	20 lithium, 20 haloperidol (33 M, 7 F)	12.5 y (median)	Lithium carbonate 900–2100 mg/day for 2 weeks	NR	OAS	Mean OAS score decreased in the lithium vs placebo group ($p = .04$); 16/20 responders (80 %) in lithium vs 6/20 (30 %) in placebo group, $p = 0.004$	Nausea, vomiting, ↑ urinary frequency
	Malone, 2000 #	RCT	20 lithium, 20 haloperidol (33 M, 7 F)	12.5 y (median)	Lithium for 4 weeks	NR	OAS (aggression)	Lithium superior ($F_{1,119} = 4.14$, $p = 0.04$); 16/20 responders vs 6/ 20 placebo ($p = 0.004$)	Nausea, vomiting, ↑ urinary frequency
	Rosebraugh, 2001	Case report	1 (NR)	13 y	Lithium sustained-release 600 mg/day + olanzapine 2.5 mg/day+sertraline 100 mg/ day	NR	NR	NR	ECG changes
	Blader, (2006)	Prospective	97 divided in five medication classes (76 M, 21 F)	5–13 y	Lithium until 12 months	NR	CBCL Externalizing, NYPRS Physical and Aggression	Lithium superior in reducing CBCL externalizing ($F_{1,26} =$ 5.23, $P = .03$) and Physical and NYPRS Aggression scores ($F_{1,26} = 4.16$, $P = .052$)	No major or clinically relevant side effects
	Masi, 2009	Retrospective	60 (46 M, 14 F)	8–17 y	Lithium for mean 8.4 months	0.8–1 mmol/L	MOAS	Mean MOAS score improved ($p < .001$; ES 1.03) between pre- vs post-treatment groups	GI, renal, endocrine and neurotoxic side effects
	Dostal, 1970	Prospective	14 (M)	11–17 y	Lithium for 8 months	6–48 mmol/L	Aggression, and psychomotor agitation	Improvement	Polydipsia and polyuria
	FitzSimons, 1981	Case report	1 (M)	6 y	Lithium carbonate 750 mg/day	NR	NR	NR	Toxicity at 5.15 mmol/ L (lethargy, circulatory collapse, purpura, thrombocytopenia, diarrhoea)
	Delong, 1987 (single longitudinal study)	Prospective	NR	NR	Lithium for mean 4.6 y	NR	Rage, aggression, encopresis	Variable improvement	NR
	Dickstein, 2009	RCT	14 lithium, 11 controls (NR)	7–17 y	Lithium for 6 weeks	0.8–1.2 mmol/ L	Mood dysregulation	No improvement	No major or clinically relevant side effects
	Ledbetter, 2015	Case report	2 (NR)	11 and 7 y	Lithium carbonate 600 mg/day	NR	Mood/ emotional dysregulation, hyperactivity	Improvement	Enuresis, polyuria
	Yuan, 2018	RCT	62 lithium carbonate, 62 calcium carbonate (NR)	4–11 y	Lithium carbonate 12 mg/kg/day	NR	IQ, LJMSSAS, CGI-I	21.3 % of the lithium group improved in IQ ($F =$ 11.03, $p = .002$), LJMSSAS ($F = 7.80$, $p = 0.007$) and CGI-I scores ($F = 82.66$, $p < 0.001$) in respect to placebo group	GI, neurological, renal, endocrine side effects (21.3 %)
	Pruccoli, 2022	Retrospective	7 (F)	mean 16 + 1.6 y	Lithium carbonate 600 mg/day for mean 1 month	NR	therapy adherence	Improvement	Renal and endocrine side effects; increase in

(continued on next page)

Table 1 (continued)

Disorder/ condition	First author, year	Design	N (genre)	Age	Type and duration of pharmacological therapy	Lithium serum level	Outcomes	Effect estimates/ Findings	Tolerability
Psychosis	Whitehead, 1970	Clinical trial	7 (NR)	5–9 y	Lithium carbonate 6–10 mg/Kg/day +placebo + thioridazine	NR	Hyperactivity, dyscontrolled behavior	No difference vs placebo	creatinine kinase No major or clinically relevant side effects
	Wood, 1989	Case report	1 (NR)	14 y	Lithium carbonate 1200 mg/day	NR	Delusions, hallucinations, psychomotor agitation	Improvement	Nephrotic syndrome
	be and Ohta, (1995)	Prospective	11 (NR)	10–15 y	Lithium 800 mg/day	NR	Positive and negative symptoms	Improvement in 8/9	No major or clinically relevant side effects
	Rachamalla, 2017	Case report	1 (M)	16 y	Lithium+clozapine up to 400 mg/ day+ citalopram+clonazepam+ atenolol	NR	Positive and negative symptoms, suicidal ideation	Improvement	Microseizure
	Fantozzi, 2022	Case report	1 (M)	16 y	Lithium ER + Lurasidone up to 111 mg/day	24 mmol/L (lithium)	Catatonia, hallucinations, mood/ behavioral symptoms	Improvement	No major or clinically relevant side effects
Suicidality	Eugene, (2024)	Retrospective	470 lithium, 5712 other antidepressants (NR)	8–17 y	Lithium	NR	Risk of suicidality	Reduced risk vs fluoxetine (aOR = 0.12, 95 % CI, 0.55–0.28)	NR

Note the table lists publications rather than studies. Two pairs of publications referring to the same study are indicated with * and #, respectively

are applicable.

2.8. Stakeholder consultation

No formal stakeholder consultation was conducted for this review.

3. Results

3.1. Selection of sources of evidence

A total of 2666 records were identified through database searches and 21 additional records through ClinicalTrials.gov. After removal of duplicates (n = 455), 2232 records were screened by title and abstract. Of these, 1865 were excluded, and 367 full-text articles were assessed for eligibility. Finally, 41 studies met inclusion criteria and were included in the review (see PRISMA 2020 flow chart in Fig. 1). A list of full-text articles that were assessed for eligibility and subsequently excluded, together with reasons for exclusion, is available in Supplementary File 2.

3.2. Characteristics of sources of evidence

The characteristics of the 41 studies included in our scoping review (reported in 43 publications), grouped by condition, in alphabetical order, are reported in Tables 1 and 2. The heat map illustrating the distribution of studies across psychiatric and neurological conditions by study type is shown Fig. 2, and the timeline showing the chronological evolution of lithium research in pediatric populations is represented in Fig. 3. Detailed checklists reporting the quality assessment via NHLBI Study Quality Assessment Tools are provided in Supplementary File 3.

3.3. Results of individual sources of evidence

3.3.1. Uses of lithium for psychopathological conditions in children and adolescents

We identified 31 publications reporting on 29 unique studies. Sample sizes ranged from 1 to 470 participants, with age spanning 3–17 years. In most studies, sex-specific distributions were not reported. The available data are summarized in Table 1. Most of the retrieved studies focused on the use of lithium to improve aggressiveness, oppositional behaviour, explosiveness, mood lability, suicidal behaviour, or emotion dysregulation, in children and adolescents with neurodevelopmental disorders, conduct disorders, or psychosis. In one case only, lithium was used to manage catatonia caused by mephedrone. We detail here the key study findings grouped by disorder, in alphabetical order.

3.3.1.1. Attention-deficit/hyperactivity disorder (ADHD). We found four studies including one double blind randomized trial (Greenhill et al., 1973), one prospective follow-up (DeLong and Aldershof, 1987), one retrospective cohort study (Bandou et al., 2010), and one case report (Licamele and Goldberg, 1989).

Therapeutic dosages of lithium carbonate ranged between 600 (Licamele and Goldberg, 1989) and 1500 mg per day (Greenhill et al., 1973). The age range of enrolled patients was 5–18 years. The number of participants enrolled ranged from one (Licamele and Goldberg, 1989) to 19 (DeLong and Aldershof, 1987). There were no studies in which controls without ADHD were included (Bandou et al., 2010; DeLong and Aldershof, 1987; Greenhill et al., 1973; Licamele and Goldberg, 1989).

In Greenhill et al. (1973), 9 children unresponsive to previous treatment for hyperactivity (which would nowadays be classified as ADHD) were placed on a three-month modified double-blind trial of lithium carbonate alternating with dextroamphetamine or placebo; lithium appeared to be efficacious only in 25 % of the cases.

DeLong and Aldershof (1987) showed that lithium was not effective in controlling symptoms of attention deficit in 19 children and treatment

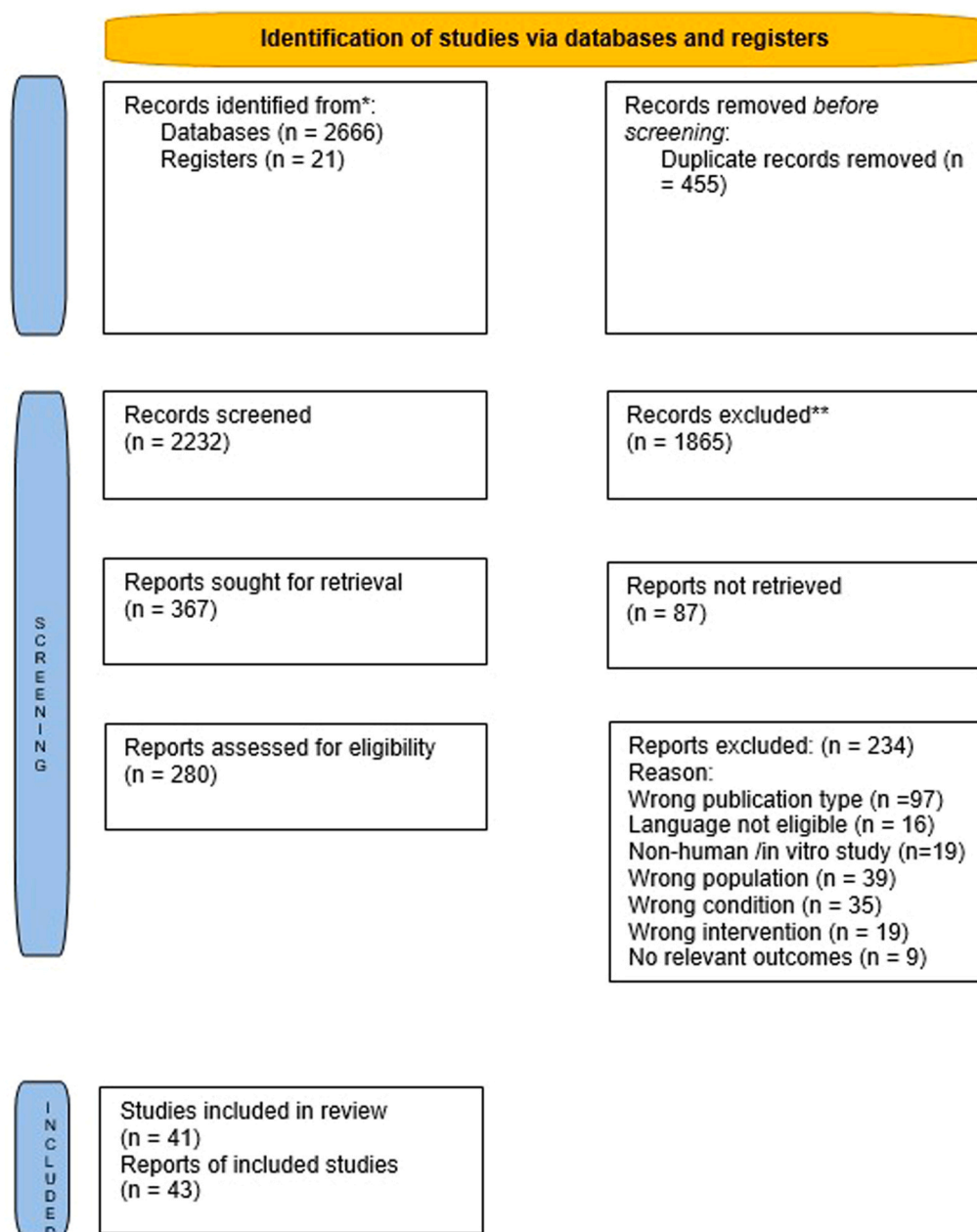


Fig. 1. PRISMA 2020 flowchart.

was typically discontinued by parents within one or two weeks. The retrospective study by [Bandou et al. \(2010\)](#) included 144 subjects (age between 5–18 years) with ADHD of whom 20 methylphenidate (MPH)-resistant subjects were divided into three treatment groups: MPH plus risperidone (n = 8); MPH plus carbamazepine (n = 5); and MPH plus lithium carbonate (n = 4). By comparing the results before and after the add-on therapy, lithium did not lead to any additional clinical improvements, based on CGI-S, in such participants (p = 0.18).

Finally, in [Licamele and Goldberg \(1989\)](#) lithium improved mood stability and conduct in a 7-year-old child with ADHD 10 days after reaching a blood level between 0.7 and 0.9 mEq/mL.

Tolerability of lithium across these studies was generally good, although [DeLong and Aldershof \(1987\)](#) reported a worsening of behavior in 8 out of 19 participants in the study.

In summary, available data, mostly from non-randomized evidence and hence prone to bias, do not provide support for the routine use of lithium in children with ADHD, for either core symptoms or associated

dysfunctions, as monotherapy or as adjunctive treatment.

3.3.1.2. Autism spectrum disorder (ASD). We found five studies, including one controlled study ([Campbell et al., 1972](#)), one prospective long-term follow-up study ([DeLong and Aldershof, 1987](#)), one retrospective study ([Mintz and Hollenberg, 2019](#)) and two case reports ([Di Vara et al., 2022](#); [Veenhuizen et al., 1992](#)).

Therapeutic dosages of lithium carbonate ranged between 450 mg ([Campbell et al., 1972](#)) and 600 mg per day ([Di Vara et al., 2022](#)). The age range of enrolled participants was 3–18 years. The number of study participants ranged from one ([Veenhuizen et al., 1992](#)) to 21 ([DeLong and Aldershof, 1987](#)).

In [Campbell et al. \(1972\)](#) lithium did not significantly improve explosiveness, aggressiveness, hyperactivity, and psychotic language compared to chlorpromazine in a sample of ten children with ASD. The participants were maintained from 7 to 10 weeks on each drug, including 3–8 weeks of maintenance at the maximum optimal dose. At

Table 2
Use of Lithium in neurological disorders in youth.

Disorder/condition	First author, year	Design	N (genre)	Age	Type of pharmacological therapy	Lithium serum level	Outcome	Effect estimates/Findings	Tolerability
Anti-NMDAR encephalitis	Wallengre, 2021	Case report	1 (F)	17 y	Lithium+olanzapine+ benzodiazepines	NR	Psychotic and manic symptoms	No improvement until I.V. Ig + metilprednisolone + teratoma removal	No major or clinically relevant side effects
Autism and LGS	Singh, 2020	Case report	1 (M)	13 y	Lithium 1500 mg/day+ Perphenazine 8 mg/day+ Quetiapine 400 mg/day +Trazodone 300 mg/day+Cannabidiol 10 mg/kg/day	NR	Aggression	Improvement	Hypersomnolence, ataxia, decreased oral intake due to toxic lithium (2.4 mmol/L)
Canavan disease	Solsona, 2012	Case report	1 (F)	3 mo	Lithium citrate for 1 year	Up to 2.75 mmol/12 h	Neurodevelopment, NAA excretion	Slowing of disease progression; 80 % ↓ urine NAA	No major or clinically relevant side effects
Head trauma	Cohn, 1977	Case report	1 (M)	12 y	Lithium carbonate 600 mg/day	NR	Agitation and emotional lability	Resolution	No major or clinically relevant side effects
KLS and other periodic hypersomnia	Goldberg, (1983)	Case report	1 (M)	17 y	Lithium carbonate 600 mg/day	NR	Periodic hypersomnia, irritability	Resolution	No major or clinically relevant side effects
	Abe, (1987)	Case report	1 (M)	15 y	Lithium carbonate 600 mg/day	NR	Periodic hypersomnia	Partial prevention of episodes	No major or clinically relevant side effects
	Muratori, 2002	Case Report	1 (M)	16 y	Lithium carbonate 1650 mg/day	NR	Periodic hypersomnia, mood, thought & behavioral symptoms	Resolution	Tremor
	Justo, 2007	Case report	1 (M)	17 y	Lithium carbonate 900 mg/day + risperidone 4 mg/day	NR	Hypersomnia, psychosis	Resolution	No major or clinically relevant side effects
	Parmar, 2017	Case report	1 (M)	10 y	Lithium carbonate 450 mg/day	NR	Hypersomnia, irritability, altered perception	Resolution	No major or clinically relevant side effects
	Hussain, 2018	Case report	1 (M)	16 y	Lithium carbonate 1000 mg/day + Lorazepam 4 mg/day	NR	Hypersomnia, hyperphagia, hypersexuality, hallucinations	Resolution	No major or clinically relevant side effects
Photoconvulsive epilepsy	Roxanas, 1996	Case report	1 (M)	16 y	Long acting 2000 mg/day +Carbamazepine 600 mg/day	NR	Mania, epilepsy	Resolution	No major or clinically relevant side effects
TSC	Gipson, 2013	Case report	1 (M)	14 y	Lithium+Everolimus+ Asenapine+Oxcarbazepine	NR	Aggression, seizures, SEGA, skin lesions	Behavioral improvement; ↓ seizures; ↓ SEGA size; improvement of angiofibromas	No major or clinically relevant side effects

NR: not reported; ↓ reduction; SEGA: Subependymal Giant Cell Astrocytoma; M: male; F: female

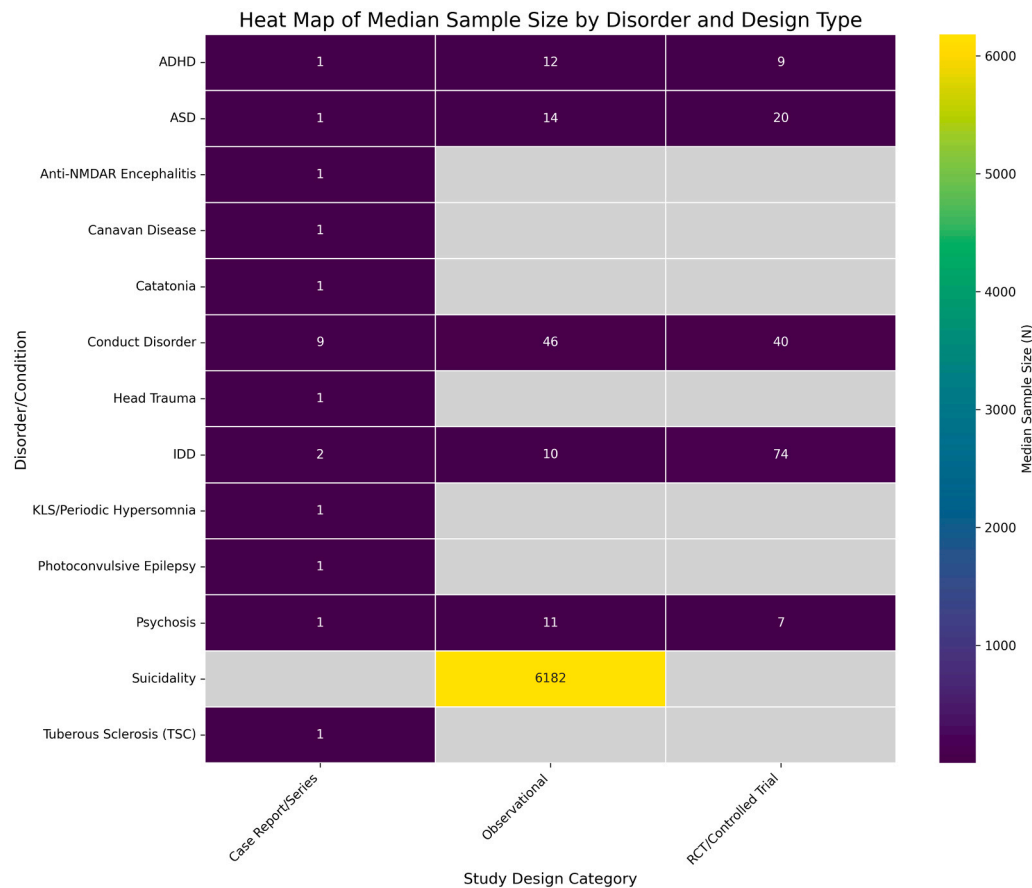


Fig. 2. Heat map of median sample size by disorder and design type.

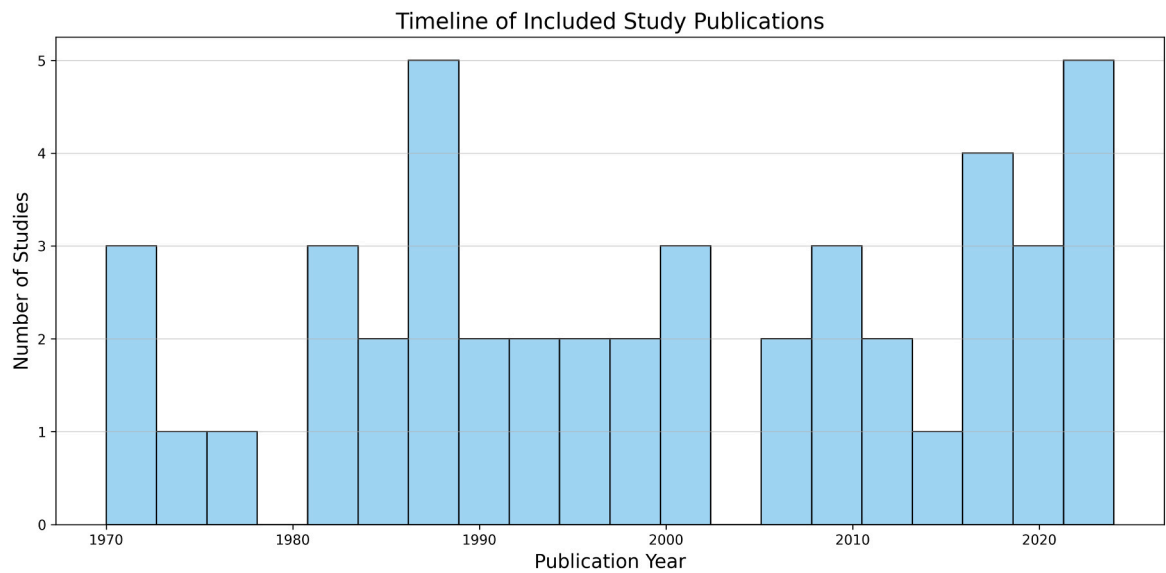


Fig. 3. Timelien of included study publications.

the end of the expected treatment period, symptoms were reduced more with chlorpromazine than with lithium and improvements were minimal with both drugs.

In the prospective study by [DeLong and Aldershof \(1987\)](#), lithium was associated with improved behavioural self-control in only six participants after a mean time of 30.6 months, while it caused a worsening in seven of them. In the retrospective study by [Mintz and Hollenberg](#)

[\(2019\)](#), 73.7 % of youths with ASD (14 participants out of 19) and concomitant maladaptive behavior improved their symptoms, based on CGI-I (rating ≤ 3), after starting lithium therapy (mean duration of treatment 495 days); among them, those with comorbid ADHD were more likely to respond ($p = 0.038$, Odds Ratio 12.2). [Di Vara et al. \(2022\)](#) described an 11-year-old child with decreased irritability and aggressiveness and improved relational and communicative abilities

after starting therapy with lithium (four weeks at serum level of 0.6 mmol/L) associated with risperidone. The 16-year-old patient described by Veenhuizen et al. (1992) experienced a reduction in exhibitionist behavior after four days of taking lithium doses of 600 mg per day.

Lithium did not lead to any major tolerability issues (Di Vara et al., 2022; Veenhuizen et al., 1992). Reversible and manageable side effects included fatigue, tremors, gastrointestinal disturbances, polydipsia, polyuria, motor excitation, and irritability (Campbell et al., 1972; Mintz and Hollenberg, 2019).

In summary, available data, in the absence of published RCTs, do not support the routine use of lithium for disruptive behaviors in ASD, but they offer some hints for future studies exploring lithium as an intervention to improve self-control.

3.3.1.3. Catatonia. We found a case report (Winerdal et al., 2024), in which 126 mg of lithium sulphate in association with lorazepam and memantine were associated, after 3 weeks of treatment, with a reduction and progressive resolution of symptoms of delayed catatonia in a 17-year-old girl with no previous contact with child and adolescent psychiatric services, nor any prior drug abuse, following intake of mephedrone. No side effects of note were reported. In the absence of RCTs or at least larger studies, there is currently no support for the use of lithium for catatonia in youths.

3.3.1.4. Conduct disorder. We found 15 studies, including five double blind trials (Malone et al., 1998; Malone et al., 2000; Platt et al., 1981; Platt et al., 1984; Rifkin et al., 1997), three prospective studies (Abe and Ohta, 1995; Blader, 2006; DeLong and Aldershof, 1987), one observational study (Carlson et al., 1992), one retrospective study (Masi et al., 2009), and five case reports/series (Fantozzi et al., 2022; Rachamallu et al., 2017; Rosebraugh et al., 2001; Vetró et al., 1985; Wood et al., 1989).

Dosages of lithium carbonate ranged between 400 mg (Rachamallu et al., 2017) and 2000 mg per day (Platt et al., 1981; Platt et al., 1984). The age range of enrolled participants was between 3 and 17 years (DeLong and Aldershof, 1987; Masi et al., 2009; Rifkin et al., 1997; Vetró et al., 1985). The number of study participants ranged from one (Rosebraugh et al., 2001) to 83 (Blader et al., 2006).

In a RCT by Platt et al. (1984), 60 children with aggressive and explosive behaviour were initially placed on placebo for a 2-week period, after which they were randomly assigned to placebo, lithium, or haloperidol treatment groups. Cognitive assessments were carried out at the end of the 2-week placebo period and again at the end of the 4-week treatment period. Lithium carbonate caused worse performance on the Porteus Maze scores compared to haloperidol and placebo groups ($F = 9.50$, $p < 0.05$ and $F = 7.81$, $p < 0.05$, respectively). No effects on other cognitive measures were found. In a previous RCT by Platt et al. (1981), hospitalized children diagnosed with conduct disorder were enrolled. After an initial 2-week placebo period to achieve sufficient drug washout, children were randomly assigned to lithium ($N = 8$), haloperidol ($N = 9$), or placebo ($N = 10$) groups. Cognitive and behavioural assessments were done at the end of the placebo period and again after 4 weeks of treatment. The results suggested that lithium had mild effects on cognition at the doses used ($t(8) = -2.73$, $p < 0.05$), with no significant changes in the placebo or haloperidol groups. In Rifkin et al. (1997), lithium or placebo was administered to 33 inpatients in a double-blind fashion for 2 weeks, with no significant differences found across clinical measures including the Overt Aggression Scale (OAS), Behavior Rating Scale (BRS), Conners Teacher Rating Scale (CTRS), or Hamilton Rating Scale for Depression (HRSD). In the double-blind, placebo-controlled trial by Malone et al. (2000), with 40 patients completing treatment, lithium was superior to placebo in reducing Overt Aggression Scale ratings over four weeks; the mean decrease difference from baseline was statistically significant, indicated by the interaction

between treatment group and time ($F_{1119} = 4.14$; $p = .04$). Sixteen of 20 participants in the lithium group were responders on Consensus ratings, compared to 6 of 20 in the placebo group ($p = 0.004$). In a previous study by Malone et al. (1998), 28 children with aggressive conduct disorder participated in a double-blind placebo-controlled trial where the Predatory Affective (P-A) index of the Aggression Questionnaire significantly differentiated responders and non-responders during treatment, regardless of lithium or placebo.

In the prospective study by DeLong and Aldershof (1987), lithium was associated with improved behavior in five of 33 children over a mean treatment duration of 21.3 months. In Abe and Ohta (1995), lithium resolved recurrent brief episodes with psychotic features in 8 of 11 children and adolescents who started lithium continuously for several weeks; when found prophylactically effective, it was administered for a week before each expected recurrence and 7–8 days thereafter to minimize side effects. In Blader et al. (2006), children receiving antimanic agents at 6-month follow-up had higher ratings relative to admission on several measures compared to those not receiving them, including adjusted CBCL Total, Externalizing, and Internalizing scores and NYPRS Total. However, at 12-month follow-up, children treated with lithium and SSRIs had significantly improved outcomes on the CBCL and NYPRS Physical Aggression and Nonphysical Disruptive Behavior subscales compared to others.

In the observational study by Carlson et al. (1992), lithium taken for at least 8 weeks was associated with reduced aggression, irritability, and self-control difficulties ($p < 0.05$), measured with the ADD-H Comprehensive Teacher Rating Scale (ACTeRS) and Teacher's Self-Control Rating Scale (TSCRS) in 11 children. In the retrospective study by Masi et al. (2009), mean Modified Overt Aggression Scale (MOAS) scores improved significantly between pre- and post-lithium treatment groups ($p < 0.001$), with an effect size of 1.03, after a mean treatment duration of 8.4 ± 2.2 months.

In the case series by Vetro et al. (1985), lithium was associated with improved extrapunitive ($p < 0.001$), implicit ($p < 0.005$), and intra-punitive aggression ($p < 0.005$), measured by Rosenzweig's Pictures Frustration Test (PFT). Wood et al. (1989) showed that, in one female adolescent, lithium combined with chlorpromazine was associated with improvement in psychosis symptoms and psychomotor agitation until a therapeutic blood level was achieved. In Fantozzi et al. (2022), lithium salts (up to 20 mmol/L) plus gabapentin were associated with a gradual improvement of catatonic symptoms over two weeks. In the case report of Rachamallu et al. (2017), lithium, in association with antipsychotics, benzodiazepines and antidepressants, was associated with a reduction of positive and negative symptoms, suicidal thoughts and an improvement of global functioning.

Across retained studies, adverse events included worsening of cognitive performance (as measured by the Porteus Maze test) (Platt et al., 1981; Platt et al., 1984), reduction in renal function (polyuria and albuminuria), gastrointestinal symptoms (abdominal discomfort, nausea, vomiting), weight gain, neurotoxic symptoms (dysarthria, trunk ataxia, horizontal nystagmus, tremor), ECG changes, polydipsia, and increased TSH (Malone et al., 2000; Masi et al., 2009; Rifkin et al., 1997; Rosebraugh et al., 2001; Vetró et al., 1985).

In summary, there is evidence from a limited number of RCTs, as well as some other studies with different designs, that lithium may improve aggressiveness in youth with conduct disorder; additional adequately powered trials are warranted.

3.3.1.5. Intellectual developmental disorder (IDD). We found seven studies, including two double-blind randomized controlled trials (Dickstein et al., 2009; Yuan et al., 2018), two prospective studies (DeLong and Aldershof, 1987; Dostal and Zvolisky, 1970), one retrospective study (Pruccoli et al., 2022) and two case reports (FitzSimons and Keane, 1981; Ledbetter and Brahm, 2015).

Therapeutic dosages of lithium carbonate ranged between 600 mg

(Ledbetter and Brahm, 2015) and 750 mg per day (FitzSimons and Keane, 1981). The age range of enrolled patients was 4–17 years (Dickstein et al., 2009; Dostal and Zvolsky, 1970; Yuan et al., 2018). The number of patients enrolled ranged from one (FitzSimons and Keane, 1981) to 62 (Yuan et al., 2018).

In the randomized controlled trial by Dickstein et al. (2009), youth who met criteria for MDS after a 2-week single-blind placebo run-in were randomized to a 6-week double-blind study of lithium (N = 14) or placebo (N = 11). No significant differences in scores of the Clinical Global Impressions–Improvement (CGI-I) and the Positive and Negative Syndrome Scale (PANSS) were observed between the two groups. In the randomized, single-center clinical trial by Yuan et al. (2018), 124 children with intellectual disabilities were given oral lithium carbonate or the same dose of calcium carbonate as placebo (N = 62/group) for 3 months. After treatment, 21.3 % of the lithium-treated children showed increases in both intelligence quotient (IQ) ($F = 11.03$, $p = 0.002$), the Infant-Junior Middle School Students Social-Life Abilities Scale (IJMSSAS) ($F = 7.80$, $p = 0.007$) and Clinical Global Impression-Improvement (CGI-I) scores, ($F = 82.66$, $p < 0.001$) but such increases were not observed in the placebo group. In prospective studies, lithium use was associated with improvement in affectivity, aggression, hyperactivity/uncontrolled behavior (DeLong and Aldershof, 1987; Dostal and Zvolsky, 1970), and encopresis (DeLong and Aldershof, 1987); unfortunately, no statistical measure was used in such studies.

In the retrospective study by Pruccoli et al. (2022) lithium use was associated with increased adherence to therapy programs in a group of 7 adolescent patients after one month. In case reports, youth treated with lithium showed an improvement in mood lability, emotional reactivity, hyperactivity and oppositional behavior between one and two months of treatment (Ledbetter and Brahm, 2015), while no data about efficacy were reported in the study by FitzSimons and Keane (1981).

Across retained studies, lithium was well tolerated with no (DeLong and Aldershof, 1987; Dickstein et al., 2009) or manageable (nausea, vomiting and decreased appetite, neurological symptoms, polyuria, hyperhidrosis, alopecia, drooling, elevated TSH blood levels, and increases in creatinine kinase) adverse events (Dostal and Zvolsky, 1970; Ledbetter and Brahm, 2015; Pruccoli et al., 2022; Yuan et al., 2018). However, serious intoxication-related side effects (lethargy and circulatory collapse) have been reported (FitzSimons and Keane, 1981) in relation to lithium serum level of 5.15 mmol/L.

In summary, available data, based on a limited number of RCTs, highlight that lithium may improve some symptoms associated with cognitive impairment, particularly uncontrolled/maladaptive behavior.

3.3.1.6. Psychosis. We found five studies including one non-randomized clinical trial (Whitehead and Clark, 1970), one prospective study (Abe and Ohta, 1995) and three case reports (Fantozzi et al., 2022; Rachamallu et al., 2017; Wood et al., 1989).

Therapeutic dosages of lithium carbonate ranged between 400 mg (Rachamallu et al., 2017) and 800 mg per day (Abe and Ohta, 1995). The age range of enrolled patients was 5–16 years (Fantozzi et al., 2022; Rachamallu et al., 2017; Whitehead and Clark, 1970). The number of patients enrolled ranged from one (Fantozzi et al., 2022; Rachamallu et al., 2017; Wood et al., 1989) to ten (Abe and Ohta, 1995).

In the clinical trial of Whitehead and Clark (1970), seven children were given lithium carbonate for periods of four to 12 weeks, alternating with four to eight-week periods of placebo. Six of the children were also given thioridazine for periods of three to six weeks. The children's behavior while taking lithium carbonate and thioridazine was compared with their behavior while on placebo. No significant differences were observed in behavior and activity level between patients taking lithium carbonate and those receiving placebo.

A prospective study by Abe and Ohta (1995) showed the remission of psychosis and affective symptoms in 8 of 9 enrolled patients initially treated continuously for several weeks; if lithium proved

prophylactically effective, it was then administered only for one week prior to each expected relapse and for 7–8 days afterward. Fantozzi et al. (2022), Rachamallu et al. (2017), and Wood et al. (1989) showed an improvement in psychomotor agitation, catatonia, suicidal ideation, psychotic, mood, and behavioral symptoms, and increased global daily functioning. No statistical analyses were reported to quantify such improvements.

No side effects were reported except for the emergence of nephrotic syndrome and, in a patient treated with lithium in combination with clozapine, citalopram, clonazepam and atenolol, microseizures (Rachamallu et al., 2017; Wood et al., 1989).

In summary, available data, mostly from non-randomized evidence, do not provide sufficient support for the routine use of lithium as monotherapy in children and adolescents with symptoms of psychosis, even though they suggest that its potential adjunctive role with anti-psychotic medications warrants further investigation.

3.3.1.7. Suicidal behaviour. We found one retrospective study (Eugene, 2024) in which, relative to adults aged 25–64 years treated with fluoxetine, lithium was associated with a reduced risk of reported suicidality in children aged 8–17 years (aROR = 0.12, 95 % CI, 0.28–0.55).

No data about dosage and tolerability were reported in the publication. In summary, available data do not allow us to draw firm conclusions on this topic.

3.3.1.8. Synthesis of results. Overall, the available literature on the use of lithium for psychopathological conditions in children and adolescents beyond mood disorders remains fragmented, methodologically heterogeneous, and often limited to small samples or single case reports. Nevertheless, some recurring themes emerged.

The clinical area in which lithium shows the most consistent evidence is conduct disorder, particularly with regard to reducing aggressiveness and severe disruptive behaviour. A handful of RCTs, although small and dated, provide converging signals that lithium may exert a beneficial effect on overt aggression and behavioural dysregulation. Regarding ADHD, findings are inconsistent. The only controlled trial available (Greenhill et al., 1973) suggested limited efficacy, and subsequent prospective and retrospective studies did not confirm substantial benefits. Isolated case reports, however, described improvements in mood stability and behavioural control, highlighting the variability of individual response but also the lack of reproducibility at a population level.

In relation to ASD, available literature is likewise inconclusive. While early controlled evidence (Campbell et al., 1972) failed to show efficacy against behavioural disturbances, more recent retrospective data (Mintz and Hollenberg, 2019) indicate that a proportion of children with ASD and comorbid ADHD may benefit from lithium in terms of behavioural regulation. Case reports also describe improvements in irritability and relational functioning, though such results remain anecdotal. Overall, lithium may be considered a potential option in highly selected cases, but the absence of methodologically sound RCTs prevents any definitive conclusion. With regard to psychosis and catatonia, the evidence is extremely sparse and limited to small uncontrolled series or single case reports. These reports suggest that lithium may play a role as an adjunctive treatment, particularly in cases with mixed affective and psychotic symptoms, or in catatonia resistant to benzodiazepines. However, the absence of robust evidence based on RCTs precludes any recommendation for clinical practice.

The evidence on suicidality is particularly striking for its scarcity, in contrast with more solid evidence in adults (Cipriani et al., 2013). However, the study by Eugene (2024) found that young patients treated with antidepressants had a significantly higher overall risk of suicidality compared to adults. Notably, lithium showed a particularly strong potential protective effect in youths. However, the retrospective design of the study limits the ability to establish a causal relationship between

lithium use and reduced suicidality.

Of note, across all diagnostic categories, the safety profile of lithium was generally acceptable, with most adverse events being manageable or reversible after discontinuation. Nevertheless, safety monitoring was inconsistently reported, and data on long-term renal, thyroid, and neurocognitive effects remain scarce.

3.3.2. Uses of lithium for neurological disorders in children and adolescents

We identified 12 publications reporting on 12 unique studies, all case reports. A total of 12 participants were included (10 males, 2 females), with ages ranging from 3 months to 17 years (mean: 13.6) (see Table 2).

We found case reports in which lithium was used with the aim of improving psychiatric symptoms of psychosis, aggression, emotional lability, mood disturbances and thought disturbances associated with several neurological conditions.

3.3.2.1. Anti-NMDAR encephalitis. We found one case report (Wallengren et al., 2021) in which lithium in association with olanzapine and benzodiazepines did not lead to improvements in psychotic and manic symptoms associated with encephalitis in a 17-year-old girl. Only the initiation of therapy with IVIG and intravenous methylprednisolone and subsequent surgical removal of an immature teratoma resolved the symptoms.

3.3.2.2. Canavan disease (CD). We found one case report (Solsona et al., 2012) showing notable improvements in neurodevelopment and significant reduction in urinary N-acetyl-aspartic acid (NAA) excretion in a 3-month-old child treated with lithium citrate up to 2.75 mL/12 h in one year. No side effects were reported.

3.3.3. Head trauma

We found one case report in which lithium, in the form of lithium carbonate and at a dosage of 300 mg per day, was used to reduce, after two days, agitation and emotional lability, until the patient resumed premorbid levels of functioning in a 12-year-old child who had suffered head trauma in the frontal region (Cohn et al., 1977). No side effects were reported.

3.3.3.1. Kleine-Levine syndrome (KLS). We found six case reports (Abe, 1987; Goldberg, 1983; Hussain et al., 2018; Justo et al., 2007; Muratori et al., 2002; Parmar et al., 2017).

In such studies, lithium was used in the form of lithium carbonate, at therapeutic dosages between 300 (Goldberg, 1983) and 1650 mg per day (Muratori et al., 2002), in monotherapy (Abe, 1987; Goldberg, 1983; Muratori et al., 2002; Parmar et al., 2017) or in association with risperidone (Justo et al., 2007) or lorazepam (Hussain et al., 2018). According to these studies, in children and adolescents between 10 and 17 years, lithium was associated with resolution (Goldberg, 1983; Hussain et al., 2018; Justo et al., 2007; Muratori et al., 2002; Parmar et al., 2017) or partial prevention (Abe, 1987) of periodic episodes of hypersomnia, irritability, hyperphagia, sexual disinhibition, mood disturbances and thought disturbances, decreased attention and concentration in a period of time between a few days (Abe, 1987) and six months (Muratori et al., 2002).

Tolerability of lithium was generally good, with no (Abe, 1987; Goldberg, 1983; Hussain et al., 2018; Justo et al., 2007; Parmar et al., 2017) or manageable side effects including tremor, increased drinking, diarrhea, and subclinical hypothyroidism (Muratori et al., 2002).

3.3.3.2. Lennox Gastaut Syndrome (LGS). We found one case report (Singh et al., 2020) in which lithium at a dosage of 1500 mg/day in association with other psychotropic drugs (perphenazine, quetiapine, trazodone, and cannabidiol) was associated with improvement in aggression for a short time in a 13-year-old patient affected by autism, severe intellectual disability and LGS. Lithium administration was

discontinued due to the appearance of side effects (hypersomnolence, ataxia and reduced oral intake) due to toxic serum lithium levels (2.4 mmol/L).

3.3.3.3. Photoconvulsive epilepsy. We found one case report (Roxanas et al., 1996) in which lithium at a dosage of 2000 mg per day in association with carbamazepine at a dosage of 600 mg per day was used to treat a 16-year-old patient with a form of photoconvulsive epilepsy leading to a remission of manic symptoms after 3 days and electroencephalographic signs of photoconvulsive epilepsy after 5 weeks. No side effects were reported.

3.3.3.4. Tuberous sclerosis (TSC). We found one case report (Gipson et al., 2013) in which lithium, in association with everolimus, asenapine and oxcarbazepine, was used with the aim of improving aggression, agitation and emotional lability having only partial satisfactory results on aggressive behaviour and mood lability in a 14-year-old patient after about one month of treatment. No side effects were reported.

3.3.3.5. Synthesis of results. In summary, evidence for the use of lithium in neurological disorders of childhood and adolescence is almost exclusively anecdotal, being derived from single case reports across highly heterogeneous conditions. In KLS lithium appeared to attenuate or prevent episodes of hypersomnia and behavioral dysregulation in a subset of cases, albeit in the absence of controlled studies. In other neurological conditions—such as anti-NMDAR encephalitis, LGS, TSC, CD, photoconvulsive epilepsy, and head trauma—findings are limited to isolated reports, with variable outcomes ranging from partial symptomatic improvement to lack of benefits. Tolerability was generally acceptable, although serious adverse events related to lithium intoxication have occasionally been described.

3.4. Study quality appraisal

As reported in detail in Supplementary File 3, across the studies for which it was possible to apply a quality appraisal tool ($n = 20$), 60 % were considered of “fair” quality and 40 % of “poor” quality. Small sample sizes and insufficient statistical power, and, in RCTs, lack of proper randomization or allocation concealment, were the main methodological concerns. Additionally, we note potential publication and language biases, and incomplete reporting of key treatment parameters—such as serum lithium levels—may limit the interpretability of individual studies.

Many of the included studies are also outdated, with substantial variation in methodology and outcome assessment, ranging from qualitative clinical impressions to standardized neuropsychological testing, further complicating comparisons and synthesis. We also highlight considerable heterogeneity in lithium use across studies. In many cases, lithium was administered alongside other psychotropic agents, and critical details regarding formulation, dosage titration, treatment duration, and serum level monitoring were often absent or insufficiently reported. This variability, combined with the intrinsic complexity of treating children and adolescents at different developmental stages and with heterogeneous disorders, limits reproducibility and precludes drawing robust disorder- or age-specific conclusions regarding safety and efficacy.

Finally, the lack of information on concurrent or recent interventions—such as psychotherapy, family-based treatments, or behavioral therapies—restricts the contextualization of reported effects and the ability to isolate lithium’s contribution.

4. Discussion

4.1. Summary of evidence

This scoping review was conducted to summarize and appraise the evidence regarding the use of lithium in children and adolescents, beyond its use as a mood stabilizer. Overall, we included 41 studies (reported in 43 articles), including clinical trials, observational studies and case series/reports, which we grouped into two main clinical groups - psychiatric and neurological conditions- in turn divided into six psychiatric (ADHD, ASD, conduct disorder, IDD, psychosis, suicidality) and seven neurological conditions (anti-NMDAR encephalitis, LGS, Canavan disease, head trauma, KLS and other periodic hypersomnias, photoconvulsive epilepsy, and TSC).

Consistent with our heat map and timeline analyses, research on pediatric lithium use has expanded over time. Even though many studies suggest that therapeutic doses of lithium can reduce emotional lability and behavioural disturbances in psychiatric and neurological conditions beyond bipolar and depressive disorders (Abe, 1987; Abe and Ohta, 1995; Assadi et al., 2010; Blader, 2006; Carlson et al., 1992; Cohn et al., 1977; Eugene, 2024; Goldberg, 1983; Greenhill et al., 1973; Licamele and Goldberg, 1989; Malone et al., 1998; Masi et al., 2009; Mintz and Hollenberg, 2019; Muratori et al., 2002; Parmar et al., 2017; Pruccoli et al., 2022; Solsona et al., 2012; Vetró et al., 1985; Wood et al., 1989; Yuan et al., 2018), the evidence is in general limited by methodological constraints, with relatively few RCTs and a predominance of anecdotal case reports, small case series, and retrospective chart reviews (Abe, 1987; Cohn et al., 1977; Di Vara et al., 2022; Fantozzi et al., 2022; FitzSimons and Keane, 1981; Gipson et al., 2013; Goldberg, 1983; Hussain et al., 2018; Justo et al., 2007; Ledbetter and Brahm, 2015; Licamele and Goldberg, 1989; Muratori et al., 2002; Parmar et al., 2017; Rachamalla et al., 2017; Rosebraugh et al., 2001; Roxanas et al., 1996; Singh et al., 2020; Solsona et al., 2012; Veenhuizen et al., 1992; Vetró et al., 1985; Wallengren et al., 2021; Winerdal et al., 2024; Wood et al., 1989; Bandou et al., 2010; Eugene, 2024; Masi et al., 2009; Mintz and Hollenberg, 2019; Pruccoli et al., 2022). Only a few controlled trials have shown efficacy, notably in reducing aggression associated with conduct disorders (Greenhill et al., 1973; Malone et al., 1998; Malone et al., 2000; Platt et al., 1981; Platt et al., 1984; Rifkin et al., 1997).

4.2. Evolution of research

Historically, lithium research in children and adolescents reflects a clear evolution in methodology and study quality. In the 1970s, studies were limited to very small RCTs and case series, often with unclear randomization, blinding, and outcome reporting, yielding preliminary and inconsistent findings (Greenhill et al., 1973; Campbell et al., 1972). Open-label trials and small single-center RCTs helped define dosing strategies and provided early efficacy signals, though sample sizes were typically fewer than 50 participants, diagnostic criteria varied, and follow-up periods were short (Youngerman and Canino, 1978; Kelly et al., 1976; Varanka et al., 1988). Monitoring of adverse events, including thyroid, renal function, and serum lithium levels, was inconsistent. During the 1980s and 1990s, controlled trials and prospective observational studies expanded, particularly in conduct disorder and ADHD, with growing attention to behavioral and cognitive outcomes, yet methodological limitations persisted (Platt et al., 1981, 1984; Rifkin et al., 1997). In the 2000s, larger prospective and retrospective observational studies with longer follow-up and increasingly standardized assessment tools provided more consistent evidence, particularly in conduct disorder, showing reduced aggression and improved behavioral regulation (Blader, 2006; Masi et al., 2009). From the 2010s onwards, research increasingly relied on large electronic health record (EHR) databases and real-world cohorts (Mintz and Hollenberg, 2019; Eugene, 2024), allowing a more comprehensive understanding of lithium's safety, tolerability, and potential anti-suicidal effects in pediatric

populations, while case reports continued to inform rare psychiatric or neurological conditions (e.g., Kleine-Levine syndrome, Canavan disease, Lennox-Gastaut syndrome).

Post-2015 studies have increasingly focused on long-term safety and off-label applications beyond bipolar disorder, such as aggression in autism spectrum disorder (Findling et al., 2011, 2013; Mintz et al., 2019), employing stronger methodologies including standardized diagnostic interviews, validated symptom rating scales, structured therapeutic drug monitoring, and longer follow-up durations. In the 2020 s, pediatric-focused studies integrated real-world data and EHR systems, enabling pragmatic research on prescribing appropriateness and monitoring, such as EHR-based reminders for serum lithium level checks (Seki et al., 2023), in contrast to pre-2000 approaches where monitoring was less standardized and reactive.

4.3. Safety and tolerability

Emerging research and clinical experience have reinforced the view that lithium treatment in youth is, in most cases, well tolerated. Across decades, most studies have reported either no side effects (Abe, 1987; Abe and Ohta, 1995; Bandou et al., 2010; Blader, 2006; Carlson et al., 1992; Cohn et al., 1977; Di Vara et al., 2022; Dickstein et al., 2009; Fantozzi et al., 2022; Gipson et al., 2013; Goldberg, 1983; Hussain et al., 2018; Justo et al., 2007; Licamele and Goldberg, 1989; Parmar et al., 2017; Roxanas et al., 1996; Solsona et al., 2012; Veenhuizen et al., 1992; Wallengren et al., 2021; Whitehead and Clark, 1970; Winerdal et al., 2024) or adverse events that can generally be managed (Campbell et al., 1972; Dostal and Zvolosky, 1970; Ledbetter and Brahm, 2015; Malone et al., 1998; Masi et al., 2009; Mintz and Hollenberg, 2019; Muratori et al., 2002; Platt et al., 1984; Pruccoli et al., 2022; Rifkin et al., 1997; Vetró et al., 1985; Wood et al., 1989; Yuan et al., 2018). Furthermore, evidence shows that even when side effects occurred due to elevated serum levels, they resolved upon discontinuation of the medication (FitzSimons and Keane, 1981; Singh et al., 2020). From a clinical standpoint, we note however that clinicians should carefully monitor risk of intoxication, especially in individuals who may take lithium in the context of suicidal ideation.

4.4. Future Research Agenda

Future research on lithium in pediatric and adolescent populations should prioritize conducting adequately powered placebo-controlled RCTs with blinded assessors and long-term follow-up. Such trials are critical to further evaluate the efficacy and tolerability of lithium in off-label indications, disentangling true pharmacological effects from natural fluctuations in symptoms or placebo responses. This body of standard trials will need to be complemented by pragmatic trials and evidence from real world data using approaches to minimise confounding (e.g., within individual designs or emulation of target trials) in large cohorts. Additionally, translational pediatric studies using advanced techniques, such as magnetic resonance spectroscopy, could provide valuable insights into its neurobiological mechanisms in the developing brain. Furthermore, pharmacovigilance studies on the effects of lithium on body systems other than the central nervous system are valuable to provide insights on possible long-term risks, e.g., to the endocrine and renal systems (Chiou et al., 2021; Yuan et al., 2021; Poels et al., 2023). From a developmental perspective, it is important to consider age-specific pharmacokinetics and pharmacodynamics, as young people differ significantly from adults in terms of body composition, renal clearance, and neurodevelopmental trajectories. Understanding these differences through modeling studies can optimize dosing strategies, enhance therapeutic effects, and minimize toxicity.

From a clinical standpoint, research into microdosing approaches represents another promising avenue. Evidence suggests that very low doses of lithium may confer neuroprotective and cognitive benefits (Strawbridge et al., 2024) but this needs further testing.

From a biological angle, biomarkers—including BDNF, IL-6, TNF- α , hippocampal volume, white matter integrity, mitochondrial function, and lithium-related gene polymorphisms such as GSK3 β —could support personalized treatment approaches and help predict individual response (Fernandes et al., 2015; Benedetti et al., 2016; Gadad et al., 2018; Chiou et al., 2021; Song et al., 2016) but to date there are no biomarkers with adequate sensitivity, specificity, positive predictive value, and negative predictive value to be used in routine clinical practice. Finally, it would be useful for future studies to include comparisons with adult populations to better understand developmental differences in response and safety profiles.

4.5. Strengths and limitations of the present review

This scoping review provides a comprehensive synthesis of off-label lithium use across pediatric psychiatric and neurological conditions, highlighting historical trends, efficacy, effectiveness, and safety profiles, as well as methodological evolution over time. Additionally, it highlights critical gaps and provides guidance for future studies.

In addition to the limitations noted for the included primary studies, some methodological limitations of our scoping review should also be noted. First, even though we endeavoured to perform a comprehensive search across a broad range of electronic databases, we cannot rule out the possibility of having missed some studies. Second, we limited the search of ongoing or unpublished studies to ClinicalTrials.gov. Third, contacting the authors to retrieve missing information from the primary studies was beyond the scope of this work, given constraints with funding. Fourth, despite no language restriction, we cannot rule out possible language bias.

5. Conclusion

Overall, although this scoping review could not support a definitive set of recommendations for lithium use in children and adolescents beyond its established role as a mood stabilizer, the available evidence suggests that the pediatric populations that may most reasonably benefit from lithium beyond its approved indications are those with severe behavioral dysregulation—particularly aggression and impulsivity in conduct disorder, ASD, or IDD. Robust evidence in psychosis, suicidality, and neurological conditions is lacking, with only anecdotal reports available. Notably, the majority of included studies ($\approx 60\%$) were single-case reports or alternatively, they included only very small sample, and only two RCTs showed mixed results, which severely limits the strength and generalizability of the conclusions. Therefore, the use of lithium across psychiatric disorders different from mood disorders should be approached with great caution and our findings should be interpreted as preliminary and hypothesis-generating. Of note, lack of evidence does not mean evidence of inefficacy. Our results should therefore be interpreted as a reflection of the lack of rigorous studies in this field. This scoping review calls for well-designed, disorder-specific trials and observational studies with designs aimed at limiting confounding, that can clarify the benefit-risk profile of lithium and support evidence-based guidelines for its off-label use in youth.

Conflict of interest & funding

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SC has declared reimbursement for travel and accommodation expenses from the Association for Child and Adolescent Central Health

(ACAMH) in relation to lectures delivered for ACAMH, the Canadian AADHD Alliance Resource, the British Association of Psychopharmacology, Healthcare Convention and CCM Group team for educational activity on ADHD, and has received honoraria from Medice.

GM declares institutional grants from Angelini, Lundbeck and Humana; advisory board for Angelini; speaker for Angelini, FB Health, Janssen, Lundbeck, and Otsuka

The other authors declare no conflicts of interest.

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Declaration of Competing Interest

Prof. Cortese has declared reimbursement for travel and accommodation expenses from the Association for Child and Adolescent Central Health (ACAMH) in relation to lectures delivered for ACAMH, the Canadian AADHD Alliance Resource, the British Association of Psychopharmacology, Healthcare Convention and CCM Group team for educational activity on ADHD, and has received honoraria from Medice.

Dr. Masi has declared institutional grants from Angelini, Lundbeck and Humana; advisory board for Angelini; speaker for Angelini, FB Health, Janssen, Lundbeck, and Otsuka

The other authors report no relevant conflicts of interest

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.neubiorev.2025.106402](https://doi.org/10.1016/j.neubiorev.2025.106402).

Data availability

No data was used for the research described in the article.

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