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The effects of L-theanine supplementation on the outcomes of patients with mental disorders: a systematic review

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Abstract

Background When utilized as an adjunct with antidepressants, antipsychotics, and other psychopharmacological drugs, certain amino acids, such as L-Theanine (LT), have shown potential effectiveness in enhancing the symptomatic outcomes of patients with mental disorders. Despite this, there is a lack of previous systematic reviews examining these associations. Therefore, we conducted a systematic review of randomized controlled trials examining these relationships.

Methods A comprehensive systematic review was conducted, scouring six electronic databases (PubMed, Scopus, PsycINFO, Web of Science, CINAHL Complete, and Cochrane) from their inception up to June 2023, specifically focusing on randomized controlled trials that investigated the effects of LT supplementation on the outcomes of patients with mental health disorders. The Cochrane Risk of Bias Tool for Randomized Trials was employed to assess the quality of the included studies.

Results Among the 419 publications identified, 11 studies from six countries — Israel, Iran, the USA, Japan, Australia, and Italy — were included in the final analysis. These studies covered a range of mental disorders, including schizophrenia, Attention-Deficit/Hyperactivity Disorder (ADHD), Obsessive-Compulsive Disorder (OCD), Major Depressive Disorder (MDD), sleep disorders, Generalized Anxiety Disorder (GAD), and Tourette syndrome. The findings demonstrated that LT supplementation reduced psychiatric symptoms more effectively than control conditions in individuals with schizophrenia, anxiety disorders, and ADHD.

Conclusions The findings from this systematic review suggest that LT supplementation significantly reduced psychiatric symptoms more effectively than control conditions in individuals with schizophrenia, anxiety disorders, and ADHD. However, further studies are essential to validate these findings, deepen the understanding of the observed effects, and explore the mechanisms underlying these associations.

Keywords L-Theanine, Mental disorders, Schizophrenia, ADHD, OCD, MDD

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Introduction

Mental disorders are psychological conditions defined by a wide-ranging change in thinking, mood, or behavior that significantly impair a person's functioning and well-being. Moreover, mental disorders are a significant public health concern [1]. Psychotherapies and pharmacotherapies are usually recommended as initial treatment approaches for mental disorders [2]. Epidemiologic evidence also suggests that L-theanine (LT) in combination with antidepressants, antipsychotics, and other psychotropic drug has potential efficacy in improving symptomatic outcomes of people with mental disorders [3, 4]. Accurate assessment of the effectiveness of research into these associations is crucial to provide valuable insights to researchers and practitioners [5].

Research suggests that LT, when taken as a dietary supplement, shows promise in alleviating symptoms associated with various mental disorders [6]. Previous studies have provided convincing evidence of its beneficial effects [4, 6–15].

In addition, the possible mechanisms underlying the effect of LT on mental health have been investigated. LT is thought to affect levels of influences neurotransmitter levels, particularly by increasing gamma-aminobutyric acid (GABA) production, which is associated with promoting relaxation and reducing stress [16]. Additionally, it may modulate other neurotransmitters like serotonin and dopamine. Numerous studies which include cell-based studies [17], animal studies [18], and clinical studies [19] have investigated the potential therapeutic effects of LT on various mental disorders, such as schizophrenia [6], ADHD [20], and others [21]. Despite the wealth of individual research papers, there remains a notable gap, which is the lack of a comprehensive systematic review summarizing all existing data, with a focus on randomized controlled trials (RCTs).

Overall, a systematic pooling of this data through RCTs—a gold standard in evidence-based medicine—is not yet established. Therefore, the focus of this systematic review is to carefully analyse and summarize data from randomized controlled trials conducted specifically in patients with schizophrenia, ADHD, generalized anxiety disorder (GAD), Tourette syndrome (TS), obsessive-compulsive disorder (OCD), and sleep disorders.

By focusing specifically on RCTs, this review aims to provide a methodologically rigorous assessment of the therapeutic potential of LT in these various mental disorders. This strategic focus on RCTs is intended to provide robust and reliable evidence on the effectiveness of LT as a potential treatment tool. The aim is to provide clinicians and researchers with evidence-based guidance for the consideration of LT in the treatment of these complex mental disorders.

Methods

To establish the effects of LT in patients with mental disorders, this systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines 2020 [22]. The study protocol was registered in the International prospective register of systematic reviews (PROSPERO) with the following registration number: CRD42023478563.

Search strategy

Six electronic databases (PubMed, Scopus, PsycINFO, Web of Science, CINAHL Complete, and Cochrane) were queried for English publications up to June 2023. The search involved utilizing various keyword combinations, which comes in Supplementary Material 1. No restrictions were imposed on these terms or any synonyms incorporated into the search approach. Additionally, we examined the citations of included studies to uncover potentially suitable articles. We also conducted a manual search of keywords on Google Scholar to identify potential studies for inclusion.

Eligibility criteria

We conducted a review of randomized controlled trials (RCTs) focusing on the impact of LT on who had been diagnosed with mental disorders as mentioned PICO criteria:

Population: The mental disorder population comprises individuals with either primary psychiatric disorders or neurodegenerative conditions, determined by clinical characteristics, with or without confirmation through biomarkers or pathology.

Intervention: LT in such a way that its dose is specified and the amount of LT can be repeated for subsequent studies. They were also included in studies that were used as additions to standard treatment.

Control: Placebo or any type of control that can be considered as standard treatment or active treatment.

Outcomes: The primary outcome for entering the study was to record and report the main symptoms of the disease based on DSM-V, but other outcomes such as biochemical and behavioral factors were also examined.

Our selection criteria excluded the following types of studies: (1) Research that explored the effects of LT in contexts unrelated to mental disorders. (2) Studies that lacked sufficient data for assessing the impact of LT on mental disorders. (3) Observational studies, reviews, editorials, conference papers, case series, or reports with fewer than four cases, qualitative study designs, and experiments involving animals. (4) Cases in which LT in the form of a published drug is packaged together with other nutrients. (5) Studies has administered LT indirectly to participants by including it in substances like

green tea, without specifying the exact dosage given to the patients.

Two investigators, SM and ES, independently identified eligible studies based on these criteria. Any disagreements were resolved through consensus or, when necessary, with the involvement of a third investigator, RM.

Study selection

Two authors, SM and ES, conducted a thorough review of potentially eligible studies by initially screening their titles and abstracts using EndNote software version 20. They adhered to predefined criteria for inclusion and exclusion to determine which studies warranted full-text assessment. The selected studies' full texts were then independently retrieved and evaluated by these same authors. Any disagreements or conflicts pertaining to the study's design, methodology, or the ultimate decision of whether to include or exclude a study were resolved by two additional authors, RM. Also, we did not exclude studies based on quality, which was due to the small number of primary articles. The number of studies included and excluded at each stage was documented and presented in a PRISMA flowchart.

Data extraction

Two authors, SM and ES, individually gathered data from the included articles. Any disagreements that arose were resolved through discussions with a third author, RM. After reviewing the included articles, further information was extracted based on the influential variables: primary author, publication year, study setting, research design, participant details, interventions, findings, side effects, and limitations.

Risk of bias assessment

The risk of bias and the quality of the included studies performed by Cochrane tool [23]. The Risk of bias-2 (ROB-2 tool) (Cochrane Risk of Bias Tool for Randomized Trials) [24]. This tool is structured in five domains (D) where the bias can be evaluated. Study quality was assessed in three categories: high risk of bias, few concerns, and low risk of bias.

Results

Study selection

Figure 1 depicts the PRISMA flow diagram. The search criteria initially yielded 419 articles from the databases based on the proposed keywords. EndNote automatically removed 173 duplicates, and 243 articles were subsequently excluded after screening the titles and abstracts. Consequently, 32 articles were included in this screening step. Following full-text evaluation, 21 articles were excluded, ultimately leaving 11 studies [4, 6–15] for final consideration.

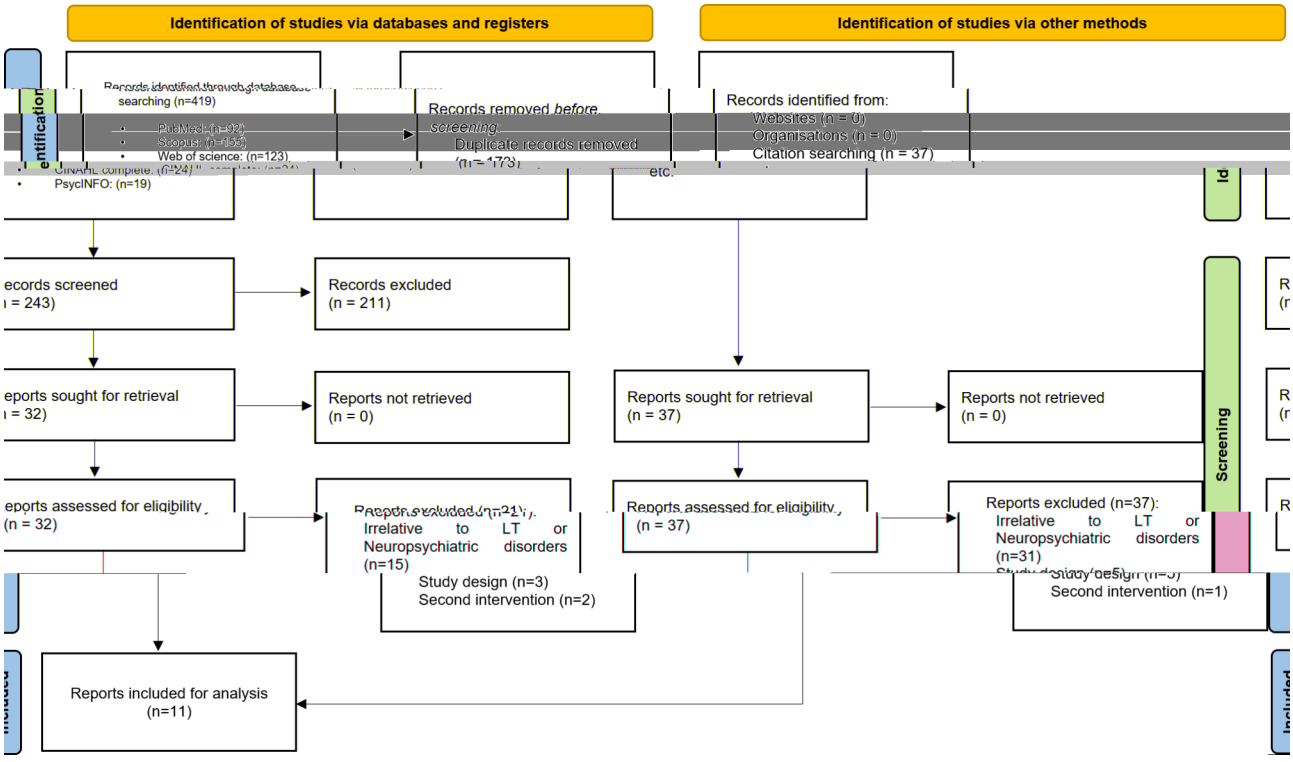

Fig. 1 PRISMA flowchart of all included studies

Risk of bias

Out of the studies considered, two exhibited a certain degree of bias risk, while nine demonstrated a low risk of bias (Supplementary Material 2). Both of the studies with some concerns had issues in the missing data value domain, while they scored high in quality across all other aspects.

Study characteristics

All studies included in the analysis were RCTs [4, 6–15], with nine employing a parallel design [4, 6–10, 12, 14, 15] and two adopting a cross-over design [11, 13]. Geographically, three studies were conducted in Israel [6, 7, 9], three in Iran [4, 14, 15], two in the USA [8, 11], and one each in Japan [13], Australia [10], and Italy [12]. Four studies focused on schizophrenia and schizoaffective disorders [6, 7, 9, 15], two on ADHD [8, 11], and one each on OCD [4], MDD [14], sleep disorders [13], GAD [10], and Tourette syndrome [12]. A total of 827 participants received LT, with both male and female subjects represented in all studies except two [8, 11]. Participant ages ranged from 9.45 to 45.5 years. LT dosages varied, including 400 mg/day (200 mg × 2 times/day) in two studies added to ongoing antipsychotic treatment [6, 7], 400 mg/day (100 mg × 2 times/day, 2 tablets/time) in another study [8], and varying dosages in the remaining studies. The majority of studies (six) had an 8-week duration [6, 7, 9, 10, 12, 15], with two lasting 10 weeks [4, 8], and one each lasting 6 weeks [14], 1 week [13], and 1 day [11] (Table 1).

Schizophrenia and schizoaffective disorder

During our investigation, we reviewed four human trials to explore the impact of LT supplementation on individuals with schizophrenia and schizoaffective syndromes. The analysis of four randomized controlled trials revealed positive outcomes across various aspects of mental health and well-being in patients. Ristner et al. [6] found that LT supplementation in conjunction with ongoing therapeutic interventions for psychosis yielded noteworthy reductions in anxiety levels ($p=0.015$), positive psychopathology scores ($p=0.009$), and general psychopathology scores ($p<0.001$) on the Positive and Negative Syndrome Scale (PANSS). However, no significant disparities were detected between the two groups regarding the PANSS negative subscale, negative factor scores, and performance on CANTAB tasks ($p>0.05$). The effects of LT were observed as early as the second week of the trial, during which LT was administered as an adjunct to ongoing antipsychotic treatment. In a related study, Miodowink et al. [7] explored the correlation between circulating levels of brain-derived neurotrophic factor (BDNF), the cortisol to dehydroepiandrosterone sulfate (DHEAS) ratio, and the favorable effects of LT in a subset of participants from the previous study. This subset underwent a trial where the same dose of LT was administered as an adjunct to current antipsychotic treatment. Changes in these biomarkers accounted for approximately 30% of the improvements observed in dysphoric mood, anxiety scores, activation factor, and dysphoric mood scores. Specifically, a decrease in serum BDNF levels accounted for 26.2% of the overall reduction in dysphoric mood ($p=0.003$) and 38.2% of the reduction in anxiety scores ($p=0.002$). Alterations in the cortisol to DHEAS ratio explained 30–34% of the variability in activation factor and dysphoric mood scores, as well as 15.9% of the changes in anxiety scores. Notably, an increase in this ratio was associated with improved activation ($p=0.004$) and dysphoric mood ($p=0.001$) scores, while a decrease was linked to reduced anxiety scores over time ($p=0.026$). Importantly, participants reported high tolerability and safety in both studies. Kardashev et al. [9] discovered that supplementing standard psychosis treatment with pregnenolone and LT resulted in enhancements in negative symptoms ($p=0.006$), anxiety levels ($p=0.008$), and general functioning ($p=0.008$) in a trial of pregnenolone and LT or placebo augmentation. The study included patients who had shown suboptimal responses to antipsychotics. The study did not find a significant correlation between positive symptoms and the combination treatment's impact. Shamabadi et al. [15] conducted a study involving 60 patients, divided into two groups. One group received a combination of risperidone and LT, while the other received a placebo. The researchers found significant reductions in negative symptoms ($p=0.03$), general psychopathology ($p=0.01$), and overall symptom severity ($p=0.04$) on the PANSS among the LT group. Importantly, the time × treatment interaction effect was significant, indicating additional improvements in negative symptoms ($p=0.03$), general psychopathology ($p<0.01$), and overall symptom severity ($p=0.04$) on the PANSS for the LT group. Notably, no adverse events were reported throughout these investigations According to the included studies, the optimal dosage of LT for schizophrenia appears to be 400 mg/day administered in divided doses as an adjunct to antipsychotic medications (Table 2).

The researchers discovered that LT influenced the concentrations of glutamate and glutamine in the frontal and parietal areas of the brain, potentially elucidating the underlying mechanisms of its therapeutic effects [15]. Abnormalities in dopamine levels within the mesolimbic and prefrontal regions of the brain are characteristics of schizophrenia. Furthermore, recent investigations have revealed that alterations in serotonin also play significant roles in the disorder's pathology [25]. Research has explored the relationships between LT and neurotransmitters dopamine and serotonin in rodent models [26,

Table 1 General characteristics of included studies

Study	Country	Design	Condition	Participants		Intervention		Duration (weeks)
				Case (N, M/F, mean age)	Control (N, M/F, mean age)	LT	Control	
Ritsner, et al. 2011 [6]	Israel	RCT	Schizophrenia or schizoaffective disorder	19, 17/2, 35.4 (11.1)	21, 14/7, 32.3 (10.2)	400 mg/d (200 mg × 2 times/d) of LT was added to ongoing antipsychotic treatment	Placebo was added to ongoing antipsychotic treatment	8
Miodownik, et al. 2011 [7]	Israel	RCT	Schizophrenia and schizoaffective disorder	19, 17/2, 35.4 (11.1)	21, 14/7, 32.3 (10.2)	400 mg/d (200 mg × 2 times/d) of LT was added to ongoing antipsychotic treatment	Placebo was added to ongoing antipsychotic treatment	8
Lyon, et al. 2011 [8]	USA	RCT	ADHD	46, 46/0, 9.45	47, 47/0, 9.74	400 mg/d (100 mg × 2 times/d, 2 tablet/time) of LT	Placebo (100 mg × 2 times/d, 2 tablet/time)	10 (6)
Kardashev, et al. 2018 [9]	Israel	RCT	Schizophrenia and schizoaffective disorder	18, 16/2, 32.2 (7.6)	21, 19/2, 33 (7.6)	Oral Pregnenolone (50 mg/day) with LT (400 mg/day) were added to a stable regimen of antipsychotic medication	Placebo was added to a stable regimen of antipsychotic medication	8
Sarris, et al. 2019 [10]	Australia	RCT	GAD (nonresponsive to their current antidepressant)	22, 4/18, 40.7 (15.0)	24, 3/21, 32.2 (9.29)	450 mg per day LT (given as one 225 mg capsule twice per day for the first four weeks of the study.	Placebo (matched for appearance, taste, and Scent with LT) for the first four weeks of the study.	8
Kahathuduwa, et al. 2020 [11]	USA	RCT (Crossover trial)	ADHD	5, 5/0, 11.87 (2.26)	5, 5/0, 11.87 (2.26)	LT (2.5 mg/kg)	1: Caffeine (2.0 mg/kg) 2: LT (2.5 mg/kg) and Caffeine (2.0 mg/kg) 3: Placebo	1 day
Rizzo, et al. 2022 [12]	Italy	RCT	Tourette syndrome	17, 15/2, 9.3 (3.9)	17, 15/2, 11.5 (2.7)	200 mg of LT and 2.8 mg of Vitamin B6	Psychoeducation (weekly sessions)	8
Nematizadeh, et al. 2023 [4]	Iran	RCT	OCD	25, 13/12, 33.88 (9.73)	25, 10/15, 31.88 (10.05)	LT (100 mg twice daily) and fluvoxamine (100 mg daily initially followed by 200 mg daily after week 5)	Placebo and fluvoxamine (100 mg daily initially followed by 200 mg daily after week 5)	10
Imafuku, et al. 2023 [13]	Japan	RCT (Crossover trial)	Sleep problems (non-depressive)	106, 38/68, 45.5 (0.7)	106, 38/68, 45.5 (0.7)	LT (200 mg/day)	1: Placebo (3300 mg of maltodextrin/day) 2: GABA (111.1 mg of barley lactic acid fermentation extract/day) 3: AVLE (50 mg/day) 4: l-serine (300 mg/day)	1 (duration of every intervention)
Shamabadi, et al. 2023 a [15]	Iran	RCT	Schizophrenia	30, 17/13, 36.43 (8.43)	30, 19/11, 33.63 (7.86)	LT (400 mg/day) and Risperidone (6 mg/day)	Placebo and Risperidone (6 mg/day)	8
Shamabadi, et al. 2023 b [14]	Iran	RCT	MDD	25, 12/13, 34.44 (5.79)	25, 16/9, 32.52 (6.47)	LT (200 mg/day) and sertraline (100 mg/day)	Placebo and sertraline (100 mg/day)	6

27]. Yamada and colleagues documented an increase of up to two-fold in dopamine levels resulting from LT infusion in the striatal region of rat brains [26]. Furthermore, Ota and colleagues noted that the daily administration of 250 mg of LT over a period of eight weeks, in conjunction with the patients' existing antipsychotic regimen, proved effective in alleviating symptoms of schizophrenia [15].

Attention deficit hyperactivity disorder (ADHD)

Our investigation delved into the profound influence of LT on individuals diagnosed with ADHD, employing two studies researching distinct aspects of the condition, with Lyon et al. [8] focusing on sleep outcomes. The group administered LT exhibited higher sleep percentages ($p<0.05$) and sleep efficiency scores ($p<0.05$). Additionally, there was a non-significant decrease in activity during sleep. Sleep quality variables, including sleep efficiency, discreet episodes of nocturnal activity, wakefulness after the onset of sleep (WASO), sleep latency, and sleep duration, were assessed using the Pediatric Sleep Questionnaire (PSQ) and actigraphy wristwatches. Analysis of data from 93 participants revealed statistically significant differences favoring LT in terms of actigraphy-measured sleep efficiency ($p<0.05$) and sleep activity ($p<0.05$). However, the study did not find significant differences in WASO ($p<0.058$) and other variables (data not provided). The PSQ data did not exhibit any significant correlations with the objective data obtained from actigraphy. Conversely, Kahathuduwa et al. [11] explored the cognitive effects of LT and made intriguing observations. Their findings indicated that LT positively impacted cognition ($p=0.04$) but appeared to worsen inhibitory control ($p=0.053$), as evidenced by increased stop-signal reaction time. Notably, the combination of caffeine and LT exhibited potential for improving the total cognition composite, enhancing inhibitory control, and reducing task-related reactivity in brain networks associated with mind wandering. These findings suggest that LT may have variable impacts on specific cognitive domains in individuals with ADHD, with the combination of caffeine and LT potentially improving certain aspects. For ADHD, the optimal LT dosage is 200–400 mg/day taken in divided doses, with combining it with caffeine potentially enhancing the effects (Table 2).

LT functions as a glutamate analogue, thereby binding to the same glutamate receptors and consequently attenuating the neuroexcitatory effects induced by glutamatergic activation [28, 29]. Dopamine and serotonin can and do interact aberrantly in ADHD at the levels of the soma, the terminals, and at a distance [30]. Yokogoshi and associates observed markedly elevated dopamine levels in the rat striatum following intragastric administration of LT, along with enhanced serotonin concentrations in the striatum, hippocampus, and hypothalamus when compared to the saline-treated control group [27]. In the study by Singh et al., LT is regarded as a potentially beneficial adjunctive therapeutic agent for children and adolescents experiencing sleep disturbances associated with ADHD [31]. There are over 300 varieties of tea derived from *Camellia sinensis* L., which are primarily categorized into three main types: green tea, oolong tea, and black tea. The LT content in a standard 200 mL cup of tea is about 25 to 60 mg of LT [32]. Furthermore, green tea, being unfermented, possesses higher concentrations of LT compared to oolong and black teas [33, 34]. Given its natural origin and widespread availability, LT presents a promising alternative for patients seeking to manage their symptoms with fewer adverse effects. Instances of liver injury linked to green tea consumption have been reported in the medical literature [35, 36]. Although these reports exist, such cases are minimal and have been documented primarily in individuals who consume excessive amounts of green tea over extended periods [37, 38].

Generalized anxiety disorder (GAD)

Sarris, et al. 2019 [10] conduct a phase II, randomized, double-blind, placebo controlled, multi-center pilot study on the effect of LT in individuals with GAD during 8-weeks. LT was administrated at 450 mg per day (given as one 225 mg capsule twice per day). Insomnia and anxiety benchmarks were measure using Insomnia Severity Index (ISI) and Hamilton Anxiety Rating Scale (HAMA) respectively. At the baseline gropes were matched on each measure except for the BAI, in which self-reported anxiety was more severe in the LT group than the placebo group ($t\ [40]=-1.73$, $p=0.092$). Based on the results no change in anxiety was found when LT administration was ceased when comparing endpoint HAMA score (Week 8; 14.59 ± 6.00) to post washout HAMA score (Week 10; 14.00 ± 5.71) in the LT group only, $t\ [16]=-0.34$, $p=0.74$. Although LT group showed lower insomnia symptoms relative to the placebo group at each visit, although this was not reflected in a significant Group × Time interaction, $F\ [1, 52]=0.90$, $p=0.35$. As the second outcome the Group × Time interaction on the MADRS for depression was found to be non-significant ($F[1,84]=0.817$, $p=0.37$), BAI ($F[1153]=0.815$, $p=0.37$). Altogether no significant adverse effect was reported between placebo and LT groups $t\ [41]=0.32$, $p=0.75$. In individuals with GAD, the optimal LT dose is 450 mg/day taken in divided administrations (Table 2).

Tourette syndrome (TS)

Rizzo, et al. 2022 [12] conduct an open-label trial to evaluate the effect of LT on patients with the diagnosis of chronic tic disorder (CTD) or Tourette syndrome (TS) over aa period of two months. Patients were distributed

Table 2 Clinical characteristics of included studies

Study	Main finding	Secondary findings	Adverse effects	Pathophysiology	Limitation	Strength	Recommendations	Conclusion
Ritsner, et al. 2011 [6]	Long-term treatment (LT) linked to reduced anxiety, lower psychopathology scores, and positive symptom relief in schizophrenia and schizoaffective disorders	LT showed no correlation with PANSS negative subscale, Clinical Global Impressions-Severity, depression, functioning, quality of life, or cognitive performance	LT was well-tolerated with no significant adverse events.	LT's chemical structure resembling L-glutamate suggests GABA agonism, elevating brain GABA levels. It increases GABA, serotonin, and dopamine, while also affecting AMPA and NMDA receptors. LT induces relaxation, influences alpha waves, dopamine, and serotonin, and impacts cell survival genes positively	Small sample size & short trial; effects of long-term (LT) treatment alone, without antipsychotic combination, weren't assessed	- Randomized double-blind placebo-controlled study - The true intention-to-treat analysis.	Further long-term, randomized, controlled studies in bigger samples are needed to justify this.	Adding low-dose lithium to antipsychotics may ameliorate anxiety, positive, and general psychopathology symptoms in schizophrenia and schizoaffective disorder.
Miodownik, et al. 2011 [7]	Adding LT in schizophrenia and schizoaffective individuals linked to improved outcomes, correlating with brain-derived neurotrophic factor and cortisol ratios	Serum BDNF levels explained reductions in dysphoric mood (26.2%), anxiety scores (38.2%), activation factor (30–34%), and awake minutes after sleep onset, but not sleep latency or duration	NR	LT treatment affects neurotrophic factors, cortisol/DHEAS ratio, dopamine release, glutamate/GABA balance, possibly neuroprotection, and variable serotonin levels in brain regions	The sample size was small. The trial duration was not long. The effects of LT alone, without being combined with an antipsychotic, were not evaluated.	- Randomized double-blind placebo-controlled study	Larger cohort with split-sample design needed for regression model. Larger trial for LT's clinical efficacy. Potential biomarkers: BDNF, cortisol/DHEA-S ratio	LT augmentation in schizophrenia may benefit from brain-derived neurotrophic factor levels and cortisol to dehydroepiandrosterone sulfate ratio, suggesting clinical effects
Lyon, et al. 2011 [8]	LT linked to better sleep quality in ADHD patients, with higher sleep percentage and efficiency scores, and reduced sleep activity tendency	LT didn't affect sleep onset or duration. A slight trend for decreased wake after sleep onset in LT group	LT was well-tolerated with no significant adverse events. A single minor side effect, a facial tic, was reported.	NR	The sample size was small. The trial duration was not long.	- Randomized double-blind placebo-controlled study	Further larger, long-term, controlled studies are needed to provide justification and explore the broader therapeutic potential of LT in ADHD patients.	LT is safe and beneficial for improving sleep quality in boys with ADHD, offering potential supplementary treatment
Kardashev, et al. 2018 [9]	Pregnenolone and LT showed enhanced negative symptoms relief by week 4 in schizophrenia patients, also reducing anxiety and boosting functionality	Pregnenolone and LT augmentation were not associated with positive symptoms, antipsychotic agents, concomitant drugs, and illness duration.	LT was well-tolerated with no significant adverse events.	LT protects brain cells by calming nerve networks, antagonizing NMDA receptors, and increasing brain-derived neurotrophic factor levels, reducing dysphoria and anxiety.	Small sample, short trial. LT effects alone weren't assessed, only as an adjunct to antipsychotics	- Randomized double-blind placebo-controlled study	Larger study required. Positive findings encourage studying pregnenolone and LT with antipsychotics in chronic schizophrenia with negative/anxiety symptoms	Pregnenolone combined with LT offers new therapy for negative/anxiety symptoms in schizophrenia/schizoaffective disorder, presenting novel therapeutic approach

Table 2 (continued)

Study	Main finding	Secondary findings	Adverse effects	Pathophysiology	Limitation	Strength	Recommendations	Conclusion
Sarris, et al. 2019 [10]	Study compared LT vs. placebo for anxiety/ insomnia. Both reduced anxiety; LT showed no extra benefit. Stopping LT didn't affect anxiety. LT improved sleep satisfaction, especially non-clinical insomnia	Study found no significant group differences over time in MADRS, BAI, PSWQ, completion times; results persisted after adjusting for covariates. No caffeine-treatment interaction	No side-effect was reported	increasing inhibitory neurotransmitter GABA, and enhance glycine and dopamine release, increasing alpha wave brain activity,	Study limitations hindered investigation of antidepressant type and dose effects due to statistical power and lack of objective sleep measurement.	1:double-blind, placebo-controlled design, use of a non-treatment one week 'run-in' period	A larger study focusing on insomnia as the primary outcome is required to confirm this finding	LT didn't aid anxiety in GAD but improved sleep satisfaction and insomnia symptoms in mild cases, suggesting potential benefits
Kahathuduwa, et al. 2020 [11]	LT enhanced cognition in ADHD patients but worsened inhibitory control. When combined with caffeine, it improved cognition and showed potential for enhancing inhibitory control.	LT, caffeine, and their mix correlated with decreased activity in the posterior default mode network during the stop-signal task	LT was well-tolerated with no significant adverse events.	LT, caffeine, or both decrease mind wandering during tasks needing inhibitory control. LT-caffeine combo lowers central executive network reactivity, aiding inhibitory control in stop-signal tasks	Small sample size, short trial duration, selective sample, strict eligibility criteria limit result generalization. Various limitations noted; caffeine, LT may affect cerebral circulation due to fMRI reliance on oxygenated hemoglobin levels	Crossover study and repeated measures design involved four measurements per participant, ensuring power to replicate prior findings	Further trials are required to assess LT-caffeine's superiority over LT or caffeine alone in treating ADHD, considering age, sex, long-term effects, and administration frequency	Combining LT and caffeine may enhance attention and cognitive performance short-term in ADHD boys, promising improved inhibitory control and reduced disinhibition
Rizzo, et al. 2022 [12]	Statistically significant differences found in tic severity between THE-group and N-group; no significant variance in anxiety symptoms ($p=0.85$)	TIQ, YBOCS, and CDI outcomes lacked statistical significance in assessing quality of life, OCD severity, and depression symptoms, respectively	No adverse effect was detected.	Conversion of glutamic acid to GABA, DOPA to dopamine, and 5-hydroxytryptophan to serotonin results in mood, cognition enhancement, and reduced stress/ anxiety	open-label design of the study, a small sample size, short follow-up period	randomized and controlled design, and thoroughly considered and implemented inclusion and exclusion criteria,	More research is necessary to validate benefits in a broader population. Trials should compare combined use of vitamin B6 and LT with individual components	Research suggests LT and vitamin B6 supplements may alleviate tics and anxiety in children with Tourette syndrome or chronic tic disorders plus anxiety
Nematizadeh, et al. 2023 [4]	Total Y-BOCS scores were lower in LTcompared to placebo group at week 5 ($P=0.039$, Cohen's $d=0.60$) and 10 ($P=0.008$, Cohen's $d=0.80$)	LT group showed significantly greater improvement in obsession scores ($P=0.007$, Cohen's $d=0.82$), with more frequent complete responses ($P=0.0001$)	Reported adverse effects: nausea, abdominal pain, headache, irritability, diarrhea, constipation; no serious effects noted in the study.	Blocks glutamate receptors, boosts GABA, serotonin, dopamine. Shows pro-cognitive, antidepressive, neuroprotective, anti-inflammatory effects by competing with glutamate	Exhaustive inclusion and exclusion criteria make that difficult to generalize its results. Low external validity	Meticulously designed, low risk of bias, High internal validity	Pragmatic trials with larger samples, crossover trials enhance insights. OCD subtype-specific studies needed for LT treatment response. Safety in CVD, CVA, pregnancy crucial	Findings in this study suggest LTas a relatively safe and effective adjuvant therapy for moderate to severe OCD.

Table 2 (continued)

Study	Main finding	Secondary findings	Adverse effects	Pathophysiology	Limitation	Strength	Recommendations	Conclusion
Imafuku, et al. 2023 [13]	All the tested supplements including placebo and LT, were found to ameliorate sleep problems significantly.	subjects who consumed dairy products often showed improvement in their sleep problems with all the tested supplements	No adverse effects were reported.	Not mentioned	No validation studies of OSA beyond Japan. No direct statistical LT vs. placebo comparison. Researchers lacked blinding	Life-habit survey, Athens Insomnia Scale recorded. Responders, non-responders separated. Uni- & multi-variate analysis predict treatment response factors	Future trials should use standard definition of insomnia and globally accepted questionnaires.	LTcan enhance sleep quality. There was no statistically significant difference between LTand placebo.
Shamabadi, et al. 2023 a [15]	LT decreased negative symptoms, general psychopathology, and total PANSS scores in schizophrenia and schizoaffective disorder patients, notably by week 4	LT was not associated with depression.	LT well-tolerated, no significant adverse events. Frequent side effects: irritability, abdominal pain, nausea (LT); irritability, diarrhea (placebo)	LT has been reported to increase dopamine levels and mitigate the neurotoxic effects caused by excessive dopamine.	The sample size was relatively small. The trial duration was not long. The effects of LT alone, not adjunct to an antipsychotic, were not evaluated.	- Randomized, double-blind, placebo-controlled design - Precise adjustment of baseline demographic and clinical characteristics	Further studies are needed considering the limitations of this study as well as preclinical and clinical research.	LT added to risperidone for chronic schizophrenia inpatients showed better safety/tolerability than placebo as adjunctive treatment
Shamabadi, et al. 2023 b [14]	A greater reduction in HDRS scores was observed in the LTgroup from baseline to weeks 2, 4, and 6 (p-values = 0.02, 0.03, and 0.01, respectively)	LTgroup, reported higher response rate (100% vs. 84%) and remitting rate (68% vs. 32%). NNT for remission in 6-week = 2.8	Both groups had similar side effect frequency including diarrhea, headache, appetite loss, vomiting, and abdominal pain, with no statistical difference	LT reduces chronic psychosocial stress, lowers HPA axis activity, inflammation, restores monoamines, and improves gut microbiota	Limited generalizability due to small sample, exclusions; short follow-up. Findings may not apply widely; caution warranted in interpretation	It was a well-designed trial with low risk of bias.	Larger studies with diverse samples needed for generalizability. Future research should consider combining LT with other therapies for enhancement	LTadjunct to sertraline outperforms placebo in treating MDD in a safe manner.

into N-group and THE-group. N-group received Psychoeducation over eight weekly sessions and THE-group received the nutritional supplements LT (200 mg/day) and vitamin B6 (2.8 mg/day) for two months. Motor and vocal tics and anxiety severity were assessed using Yale Global Tic Severity Rating Scale (YGTSS) and Multidimensional Anxiety Scale for Children (MASC) questionaries respectively. First of all, LT didn't cause any side effect over the duration of the trial. Results showed a significant difference between the THE-group versus N-group in the severity of tics as assessed by YGTSS at the end of the course ($p=0.0460$). On the other hand, no significant difference was observed between the THE-group versus N-group in the severity of anxiety symptoms based on MASC ($p=0.85$). In conclusion, for Tourette syndrome, the optimal LT dosage is 200 mg/day (Table 2).

Obsessive compulsive disorder (OCD)

In the sole RCT investigating the augmentative impact of LT in conjunction with fluvoxamine, Nemati Zadeh et al. [4] conducted a 10-week multicenter, parallel-group, placebo-controlled study involving adult patients (18–60 years) with a Y-BOCS score exceeding 21, excluding those with a history of psychotropic medication or psychotherapeutic interventions within 6 weeks prior to the trial. Rigorous exclusion criteria eliminated patients with psychological co-morbidities, treatment resistance, and low intelligence. All participants received fluvoxamine, with random allocation to LTor placebo. The primary outcome, assessed using the Y-BOCS scale at baseline, weeks 5 and 10, revealed a significant improvement in obsession subscale scores in the LTgroup compared to placebo at week 5 (MD= -3.52, 95% CI[-6.85, -0.19], $P=0.039$) and week 10 (MD= -5.12, 95% CI[-8.77, -1.46], $P=0.008$), indicating a moderate effect size (Cohen's $d\geq0.6$). No significant differences were noted in the compulsion subscale. The LT group exhibited a higher complete response rate (92 vs. 36%, p-value=0.0001) and a trend toward a higher remission rate (44 vs. 16%, p-value=0.0622), with no significant differences in side effect rates. In conclusion, this RCT suggests that LT, in combination with fluvoxamine, may offer benefits for obsessive-compulsive symptoms, particularly in reducing obsessions, without notable increases in adverse events In OCD patients, 200 mg/day LT taken alongside an SSRI antidepressant is the optimal dosage (Table 2).

Sleep disorders

In a recent self-controlled, randomized, cross-over trial with six arms [13], The study sought to evaluate the impact of different active ingredients (LT[200 mg/day], GABA [111.1 mg/day], Apocynum Venetum leaf extract [50 mg/day], or l-serine [300 mg/day]), a placebo (3300 mg/day of maltodextrin), and a session of mindfulness psychotherapy on sleep among healthy individuals with significant sleep disturbances determined by the Pittsburgh Sleep Quality Index (PSQI). The trial included non-smoking, non-drinking, full-time workers planning to stay at home, with participants having sleep issues (PSQI score ≥5) and no depression (Beck Depression Inventory (BDI) ≤16). Stratified randomization ensured comparable PSQI and BDI scores. Employing a cross-over design, the study consisted of a 9-day pre-observation period, six 7-day intervention periods, and five 7-day washout periods. Supplements, placebo, and mindfulness were administered before bedtime. Sleep quality, assessed using the Oguri–Shirakawa–Azumi (OSA) sleep questionnaire, demonstrated scores reflecting sleep quality before and after each treatment, with mean scores compared to the pre-observation period using a before-after analysis. The study lacks evidence on the reliability or validity of the intervention in English literature and did not directly compare intervention and placebo arms. Across all 6 study arms, a significant increase in OSA total score was observed. Focus on LT and placebo arms revealed LT significantly increased scores in Sleepiness on rising (OSA-1), Initiation and maintenance of sleep (OSA-2), Refreshing (OSA-4), and length of sleep (OSA-5). Placebo also increased OSA-1, OSA-2, and OSA-4 scores significantly. However, no statistically significant difference between LT and placebo in any OSA score domain was found using an independent t-test on reported mean changes and SEM. The optimal LT dosage for sleep disorders is 200 mg/day taken at bedtime (Table 2).

Major depressive disorders (MDD)

In a recent 6-week, randomized, controlled trial assessing LTaugmentation of sertraline in individuals with MDD [14]. The study, detailed in Table 2, adhered to DSM-V criteria for MDD diagnosis, enrolling patients with a 17-item Hamilton Depression Rating Scale (HDRS) score exceeding 19 and excluding those with various criteria such as recent antidepressant use, electroconvulsive therapy, psychiatric comorbidities, suicidal ideation, and substance abuse. Notably, patients exhibiting exaggerated symptoms during treatment were excluded without specifying the number. Primary outcomes focused on HDRS score changes, with secondary outcomes encompassing early response, treatment response, remission rates, time to treatment response, and adverse events. Among 60 sertraline-treated participants randomly assigned LT(200 mg/day) or placebo, 50 completed the study. While no significant differences emerged in HDRS mean scores at week 2, weeks 4 and 6 displayed significantly lower scores in the LTgroup, accompanied by higher response rates (100% vs. 84%) and remission rates

(68% vs. 32%). The study highlighted a notable Number Needed to Treat of 2.8, indicating the requirement of LTover placebo for an additional patient to achieve remission at six weeks. For major depressive disorder, the optimal L-theanine dosage appears to be 200 mg/day used as an adjunct to antidepressant medication (Table 2).

Discussion

This comprehensive systematic review, the first of its kind in the field, revealed a scarcity of studies addressing the effects of LT on reducing the symptoms of various mental disorders, including schizophrenia, ADHD, OCD, MDD, sleep disorders, GAD, and Tourette syndrome. The comprehensive examination demonstrated that LT supplementation significantly alleviated psychiatric symptoms effectively, notably in individuals with schizophrenia, anxiety disorders, and ADHD, though the effect was not consistent across all investigated disorders. Our findings suggest a promising role for LT in mitigating symptoms of specific mental disorders. However, caution is warranted, emphasizing the need for further studies to validate these initial outcomes, deepen our understanding of observed effects, and elucidate underlying mechanisms. This review provides crucial insights into the potential therapeutic applications of LT, highlighting the imperative for additional well-designed investigations to establish the reliability and generalizability of observed outcomes.

While our systematic review highlights the promising potential of LT in mitigating symptoms across several mental disorders, the elucidation of its precise mechanisms remains an area requiring further exploration. Animal studies have provided valuable insights into the potential mechanisms through which LT may exert its therapeutic effects in mental disorders. A study on rats demonstrated that LT administration increased monoamine neurotransmitter levels, including serotonin, norepinephrine, and dopamine, in key brain regions such as the prefrontal cortex, hippocampus, and nucleus accumbens [39]. These changes were associated with a reduction in depressive behaviors in the animals. Furthermore, in a cohort of cats, LT was found to significantly reduce stress-related behaviors, such as inappropriate urination, fear-induced aggressiveness, and hypervigilance, with notable improvements observed after 30 days of supplementation [40].

LT, an amino acid predominantly found in tea leaves, has been recognized for its ability to cross the blood-brain barrier, suggesting a direct impact on the central nervous system. One proposed mechanism involves the modulation of neurotransmitter activity, particularly the augmentation of gamma-aminobutyric acid (GABA) levels [6, 29, 41]. The LT functions as a GABA agonist, thereby elevating brain GABA levels, which in turn influences dopamine and serotonin levels [29].

Furthermore, LT has demonstrated its impact on various neurotransmitter systems, including serotonin and dopamine [42]. These neurotransmitters play pivotal roles in regulating mood, and imbalances in their levels have been linked to various mental disorders [43–45]. The ability of LT to influence these neurotransmitters may contribute to its observed effectiveness in alleviating symptoms associated with depression, anxiety, and attention-related disorders [15, 42, 46–54]. Research indicates that LT triggers the release of dopamine in the striatum by interacting with glutamate receptors and inhibits the reuptake of glutamate, leading to a notable increase in GABA concentration [16]. Additionally, it is suggested that LT has neuroprotective effects in the hippocampus by blocking NMDA and AMPA receptors [29, 55]. In a separate study, Kardashev et al. proposed that LT may shield brain cells from excitotoxicity by calming nerve networks in the brain [56]. The study also revealed that LT acts as an antagonist on NMDA receptors [55], elevates BDNF levels [7], and exerts modulatory effects on GABA, NMDA, sigma-1, cholinergic, and dopamine receptors [56–58].

Furthermore, LT's impact on alpha brain wave activity deserves consideration. Increased alpha wave activity is associated with a state of relaxed alertness, and alterations in these patterns have been linked to various mental disorders [32, 59]. The modulation of alpha wave activity by LT may contribute to its anxiolytic effects and improvement in attention-related symptoms [60].

While these proposed mechanisms provide plausible explanations for the observed effects of LT, it is essential to acknowledge the complexity of mental disorders. The interplay of various neurobiological factors and the specificities of each disorder warrant in-depth investigations to unravel the precise pathways through which LT exerts its therapeutic effects. Future research endeavors should focus on unraveling these intricate mechanisms to solidify the understanding of LT's potential as a valuable adjunct in the management of mental disorders.

The use of LT as an alternative treatment is increasing due to its accessibility. Unlike many other medications, LT is widely available over the counter as a dietary supplement [61]. This makes LT an appealing option for patients looking for non-prescription or adjuvant treatments that can be easily integrated into their existing treatment regimens. For instance, a clinical trial demonstrated that LT, when used as an adjuvant to fluvoxamine, significantly improved obsession-related symptoms in patients with moderate to severe OCD compared to fluvoxamine alone [4]. Moreover, LT has been noted for its safe side effect profile compared to conventional psychiatric medications. While medications

such as antipsychotics and benzodiazepines are effective, they are often associated with considerable side effects, including sedation, weight gain, and metabolic disturbances [62, 63]. LT, on the other hand, has been shown to have a much milder side effect profile, with no significant adverse events reported in the literature [64, 65]. This makes LT an attractive candidate, particularly for long-term management.

While our review shows the potential benefits of LT for reducing symptoms of mental disorders, it's important to recognize that some studies have reported different findings. For instance, a study evaluating LT in a rat model of PTSD found no significant improvements in neurobehavioral functions related to anxiety or memory, suggesting that LT may not be effective in preventing or treating PTSD symptoms [66]. Similarly, Sarris et al. found that adjunctive LT did not significantly reduce anxiety symptoms in patients with GAD compared to placebo, indicating limited efficacy for anxiety in this population [10]. These differences show that LT's effects vary across conditions and highlight the need for more controlled studies to better understand its benefits and limitations.

In another area of research, studies on healthy adults show that LT can effectively manage stress and enhance cognitive functions. For instance, in a study by Moulin et al., LT supplementation significantly decreased perceived stress and improved sleep quality in healthy individuals with moderate stress after 28 days, while also enhancing cognitive attention and reaction times [67]. Additionally, as demonstrated by Evans et al., a single dose of LT led to increased alpha wave activity in the brain, suggesting a calming effect during acute stress [68]. However, some research indicates that LT incorporated into food products may not have significant effects on physiological responses such as blood pressure and heart rate [69]. Overall, LT shows promise for improving mental health and cognitive performance, but more research is needed to understand its effects in various situations.

Strengths of the current review

Firstly, the foremost strength lies in the novelty of this systematic review, marking it as the inaugural exploration of the effects of LT across a diverse spectrum of mental disorders. This pioneering aspect not only contributes significantly to the existing body of literature but also establishes a foundation for future research in this emerging field. Secondly, the review exhibits a comprehensive analysis that spans a range of mental disorders, including schizophrenia, ADHD, OCD, MDD, sleep disorders, GAD, and Tourette syndrome. This breadth in coverage enhances the study's applicability and relevance to a wide array of psychiatric conditions, providing a holistic perspective on the potential impact of LT supplementation. Additionally, the adherence to rigorous methodology, following the PRISMA guidelines, instills confidence in the reliability and validity of the study's conclusions.

Limitations of the current review

First and foremost, among the limitations is the constrained number of studies available for analysis. This scarcity restricts the breadth and depth of the conclusions drawn, emphasizing the need for more extensive research in this area. Secondly, the heterogeneity observed in population characteristics, and outcome measures introduces complexities in comparing and synthesizing results. This heterogeneity poses challenges in establishing consistent patterns of LT's effects across different mental disorders. Additionally, the lack of standardized dosages and potential publication bias further underscore the importance of interpreting the findings with caution. Despite these limitations, the review serves as a valuable starting point, shedding light on potential avenues for future research to address these challenges and enhance our understanding of LT's impact on mental disorders.

Conclusions

In summary, this pioneering systematic review marks the first comprehensive exploration into the effects of LT on a spectrum of mental disorders. The study's strength lies in its novelty, offering a groundbreaking examination of an under-researched area, and its broad analysis covering diverse disorders. Notably, LT supplementation demonstrated promising efficacy in reducing psychiatric symptoms, particularly in schizophrenia, anxiety disorders, and ADHD. However, the review is not without limitations. The scarcity of studies, potential publication bias, and the lack of standardized dosages underscore the need for cautious interpretation. While the findings suggest a potential role for LT in certain mental disorders, these conclusions warrant validation through further well-designed studies. Despite the current constraints, this review contributes valuable insights into the therapeutic potential of LT. Future research should focus on addressing the identified limitations, exploring individual conditions separately, standardizing dosages, and investigating the intricate mechanisms underlying LT's effects. This study serves as a crucial stepping stone, laying the groundwork for a more nuanced understanding of LT's impact on mental health and offering avenues for more targeted and effective interventions in the future.

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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RM initiate the concept and conduct the initial investigation. AS and ES conduct the evaluation and incorporate the findings; and in addition to SM are responsible for composing the initial draft. Oversight throughout all stages is provided by GA. The final version for publication is approved by all authors.

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