Neuropsychiatric Disease and Treatment

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REVIEW

Current Evidence of Acetyl-L-Carnitine Use in Mood Disorders-: A Systematic Review and Meta-Analysis

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Abstract: Acetyl-l-carnitine (ALC) is increasingly recognized for its potential psychopharmacological mechanism and role in the treatment of mood disorders, particularly major depressive disorder (MDD) and bipolar disorder (BD). Emerging evidence suggests that ALC levels are reduced in individuals with MDD, and this deficiency may contribute to depressive symptoms through disruptions in mitochondrial fatty acid transport, neuroplasticity, and neurotransmission. This review synthesizes findings from randomized controlled trials, open-label studies, and observational research examining ALC use and clinical outcomes in adults treated with ALC in MDD and BD. A systematic review (n=15) and meta-analysis (n=10) studies (14 randomized controlled trials [RCTs] and 1 open label) involving 809 participants (treatment group: 392; comparator group: 417) revealed that ALC significantly reduces depressive symptoms compared to placebo, with comparable efficacy to standard antidepressants and fewer adverse effects. Subgroup analyses suggest enhanced benefits in older adults and those with treatment-resistant depression. These findings support the potential of ALC as both a biomarker and a therapeutic agent in mood disorders. Further large-scale, longitudinal studies are needed to clarify its clinical utility and mechanistic pathways in mood disorders.

Keywords-: acetyl-L-carnitine, ALC, mood disorders, major depressive disorders, bipolar depression, personalized medicine

Introduction

Major depressive disorder (MDD) is the most prevalent psychiatric disorders globally and leading cause of disability, affecting >280 million people worldwide.[1] Despite the availability of multiple treatments, a substantial proportion of patients either fail to achieve remission, particularly in cases of treatment-resistant depression (TRD) and late-life depression.[2] While the monoamine hypothesis has dominated MDD treatment and research arena, however it has significant limitations too.[3] Typical antidepressants affects neurotransmitters, with delayed clinical benefits.[4]

Despite the availability of multiple antidepressant classes, TRD remains common, and many patients experience incomplete remission or intolerable side effects.[2,5] These limitations underscore the urgent need for newer approaches to broaden MDD/TRD treatment options. This highlights the critical need for novel, well-tolerated, and with alternative mechanisms to broaden MDD treatment options, especially Acetyl-L-Carnitine (ALC). This potential of ALC has emerged as a promising candidate due to its neuroplasticity-enhancing, mitochondrial, and epigenetic effects.[6–9]

ALC a naturally occurring endogenous short-chain acetylated derivative of L-carnitine which plays a critical role in mitochondrial energy metabolism by facilitating the transport of long-chain fatty acids across the mitochondrial membrane.[10] ALC has pivotal role beyond its metabolic functions in neuroprotection, antioxidant, and have neurotrophic properties.[6] Past literature provides substantial evidence for its potential role as an antidepressant, especially in older adults and individuals with treatment-resistant mood disorders. A recent meta-analysis study reviewed twelve randomized

https://doi.org/10.2147/NDT.S586506
Received: 6 January 2026
Accepted: 12 March 2026
Published: 3 June 2026

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controlled trials (RCTs) (n = 791) and found that ALC supplementation significantly reduced depressive symptoms in MDD as monotherapy and augmentation compared to placebo, with effect sizes comparable to standard antidepressants and a superior safety profile.[11] Interestingly, the antidepressant effects of ALC appeared most robust in older adults, suggesting age-related differences in mitochondrial or neurochemical pathways might mediate its psychotherapeutic actions.

Mechanistically, ALC exerts its antidepressant effects via multiple pathways, including enhancement of mitochondrial function, upregulation of brain-derived neurotrophic factor (BDNF), modulation of glutamatergic neurotransmission, and epigenetic regulation of gene expression involved in mood regulation.[12] Preclinical data also have shown that it rapidly increases mGlu2 receptor expression via histone acetylation, leading to sustained antidepressant-like effects.[9] Furthermore, ALC was shown to be as effective as the antidepressant amisulpride, with fewer side effects and better tolerability in older adults too.[13] Another study found that patients with MDD had significantly lower plasma levels of ALC compared to healthy controls, and these levels were inversely correlated with depression severity and duration.[6] ALC has been used as an adjunct treatment for bipolar depression (BD), however no significant benefits noted in improvement in depressive symptoms.[14] ALC also crosses blood-brain barrier (BBB) more efficiently than its free carnitine molecule, which has potentially stronger antidepressant effects compared to non-acetylated forms.[10] Interestingly, ALC may help alleviate depression in older adults, potentially by restoring phosphomonoester levels in the prefrontal cortex to normal.[15] Overall, it favors that ALC could serve as a potential treatment and plays role as a potential biomarker for MDD.

In summary, current clinical and preclinical evidence supports the antidepressant properties of acetyl-L-carnitine, particularly in populations with treatment-resistant depression, and cognitive impairment in mood disturbances. Its multimodal mechanisms of action and excellent tolerability make it a promising candidate for adjunctive or standalone treatment in mood disorders. Further large-scale, longitudinal studies are warranted to clarify its efficacy, optimal dosing, and patient selection criteria. There is a lack of consistent data and evidence regarding an optimal use of ALC in treatment of depression. Thus, we aimed to conduct this systematic review to appraise the current evidence for ALC use in the treatment of depression in mood disorders.

Methods

A protocol was developed for this systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[16] The protocol was registered with PROSPERO[17,18] (CRD420250391405).

Data Sources and Search Strategies

A comprehensive search of several databases was performed on October 24, 2022, and updated December 10, 2024. No date limits were applied to the search. Animal studies were excluded. Databases searched (and their content coverage dates) were Ovid MEDLINE(R) (1946+ including epub ahead of print, in-process, and other nonindexed citations), Ovid Embase (1974+), Ovid APA PsycInfo (1967+), Ovid Cochrane Central Register of Controlled Trials (1991+), Ovid Cochrane Database of Systematic Reviews (2005+), Web of Science Core Collection via Clarivate Analytics (1975+), and Scopus via Elsevier (1974+). These articles were reviewed through Covidence platform as provided by Mayo Clinic Libraries.[19]

The search strategy was designed and conducted by a medical librarian (L.C.H.) with input from the study's principal investigator. Controlled vocabulary supplemented with keywords was used to search for studies on evaluating ALC use in patients with mood disorders. The search strategy listing all search terms used is available in the Appendix 1.

Study Selection

Two reviewers (R.K. and Z.H.) working independently and in pairs identified and screened the titles and abstracts of potentially eligible articles. Subsequently, the full texts were reviewed separately by two different reviewers (R.K, Z.H, R.S and S.S). Any disagreement was resolved by consensus with other coauthors. Inter-reviewer agreement during study selection was assessed using percent agreement. In cases where multiple studies originated from the same cohort, the study with the larger sample size was selected. Eligible studies included those involving adult patients diagnosed with a mood disorder ie., MDD or BD and receiving pharmacological treatment with ALC, either as monotherapy or as an adjunctive treatment. Studies were included if they reported outcomes related to remission or response rates, all-cause discontinuation, or changes in symptom severity using standardized behavioral scales. Eligible study designs included

RCTs, open-label studies, non-randomized studies, and observational studies. Preclinical studies, case series, case reports, and review articles were excluded. Inclusion/Exclusion Criteria and Adverse Events were listed in Table S1a.

Data Collection

Data were extracted from the included studies using a standardized data extraction form by 2 reviewers. We extracted data on the following variables: study characteristics (author, year, country, study design, sample size, demographic characteristics of study participants, inclusion and exclusion criteria), intervention types, outcome measures, and duration of treatment (weeks). To standardize the ALC values across the studies, we converted all the data values to grams per day (g/day).

Methodological Quality and Risk of Bias Assessment

We used the Cochrane Risk of Bias 2 (RoB 2) tool (crossover extension where applicable) for assessing the risk of bias to evaluate the methodological quality of RCTs.[20] We assessed the risk of bias for randomization process, deviations from intended interventions, missing outcome data, measurement of outcome, selection of reported results, and other biases. For the non-randomized/observational studies, the methodological quality was assessed using Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I).[21] The certainty of evidence for key outcomes was assessed using GRADE (risk of bias, inconsistency, indirectness, imprecision, and publication bias).[22]

Data Analysis

Quantitative synthesis was conducted using randomized controlled trials with extractable outcome data. We pooled continuous depressive-symptom outcomes based on standard scales used by studies ie. Hamilton Depression Rating Scale (HDRS),[23] Beck Depression Inventory (BDI),[24] and Montgomery–Åsberg Depression Rating Scale (MADRS)[25] as standardized mean differences (SMDs) and their corresponding 95% CI at end-of-treatment (negative values favor ALC) using random-effects (REML) models. The outcome was the change in depressive symptom severity from baseline to end-of-treatment. We extracted outcomes for all reported standard scales; however, where a study assessed depression on multiple scales, we prioritized the HDRS for the primary meta-analysis, using one effect per study. Heterogeneity was quantified with Cochran's Q-test, I^2, and τ^2 statistics. Small-study effects were examined via funnel plots, Egger's regression, and Begg's rank test, with trim-and-fill used as sensitivity analysis when indicated. Subgroup analysis was done by stratifying studies by comparator groups (1) ALC monotherapy vs placebo; (2) ALC + add-on vs the same add-on; (3) ALC vs another drug; and (4) ALC + add-on vs placebo, and by age (studies primarily enrolling ≥60 vs <60 years), with random-effects models within strata and Q_between to compare subgroups. Also, a meta-regression analysis was conducted to evaluate the treatment duration and ALC daily dose as moderators in the HDRS and BDI datasets. Also, since depressive outcomes were assessed with different rating scales, we grouped them based on the scales most frequently used and performed a secondary meta-analysis within the HDRS (n=9), BDI (n=4), and MADRS (n=3) groups. Each of these scales was analyzed separately using one effect per study at the end-of-treatment time point. Safety outcomes (adverse events) were synthesized descriptively because AE reporting was incomplete and not sufficiently consistent across trials to support quantitative synthesis. All analyses were conducted in Stata software version 17, and p-values below 0.05 were considered statistically significant.

Results

Study Selection

A total of 195 records were initially identified through database searches. After removing duplicates and screening titles and abstracts, 27 full-text articles were assessed for eligibility. Ultimately, 14 RCTs[10,11,15–26] and one open-label clinical trial[12] met the inclusion criteria. Ten trials[13,14,26–32] had sufficient data for the meta-analysis (n=366 treatment, n=359 control), and five trials[15,26,33–35] were excluded from quantitative synthesis due to incomplete or non-extractable data. Only randomized trials contributed to quantitative synthesis. The selection process is summarized in the flow diagram (Figure 1).

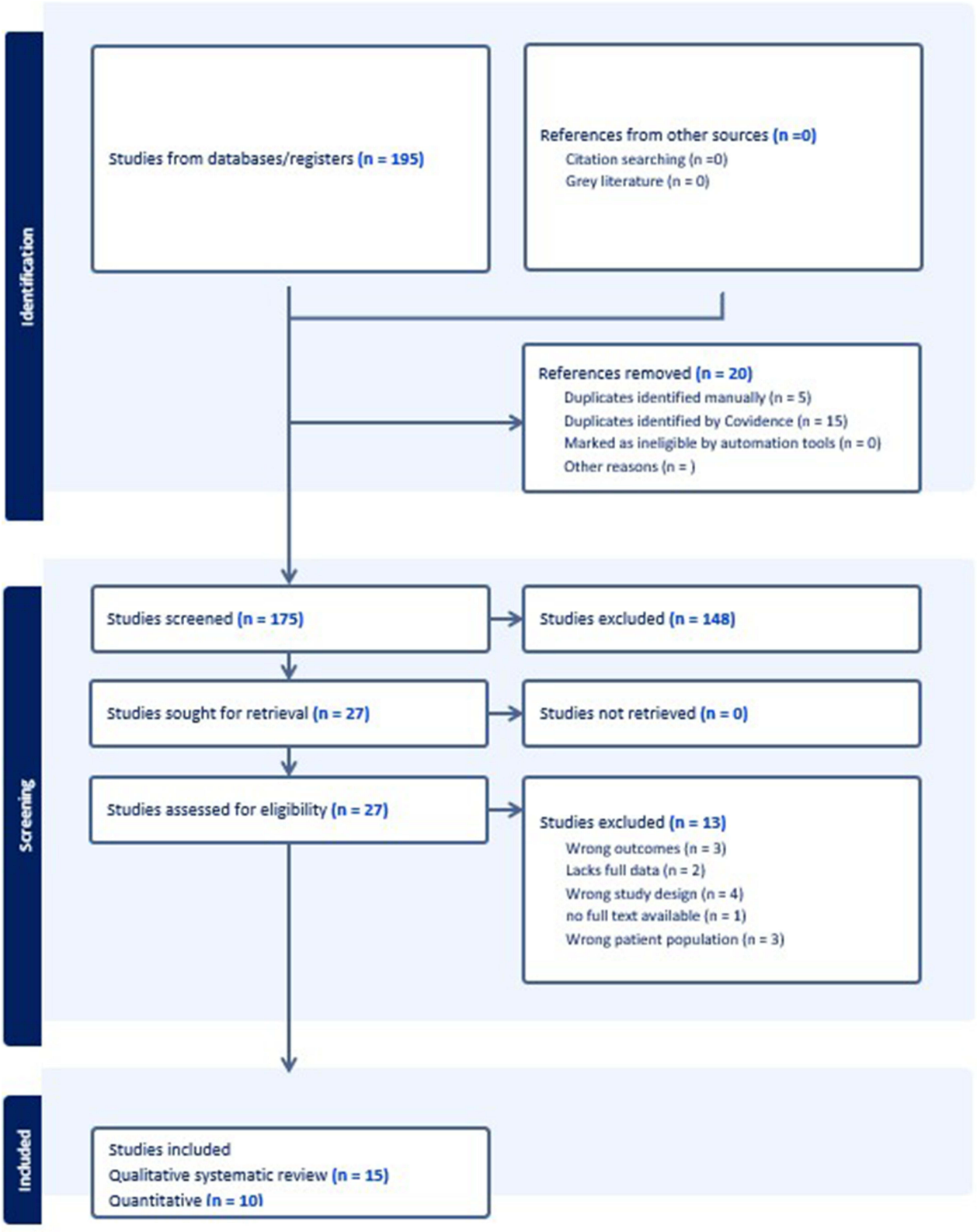

Figure 1 PRISMA flow diagram.

Study Characteristics

The 15 included trials were conducted across Italy (n=9), the United States (n=3), Russia (n=1), Iran (n=1), and India (n=1), and were published between 1983 and 2024. Fourteen were RCTs, including one crossover trial,[21] and one trial was open label.[12]

All except one were published in English and we used translated version for data verification.[19] Across the included studies, sample sizes ranged from 8 to 193 participants, and participants' ages ranged from 18 to 93 years. The total number randomized, and gender distribution were not consistently reported; however, among trials that reported gender, females comprised the majority. Depressive outcomes were evaluated using various assessment tools, among which HDRS, BDI, and MADRS were most frequently used. The treatment duration ranged from 40 days to 12 weeks, and daily doses of ALC varied from 1–3 g/day.

Diagnostic criteria applied across the included studies varied by disorder. Five studies enrolled participants with MDD,[16,17,19,20,25] and four focused on dysthymic disorder (DSM-IV criteria).[10,15,18,23] One trial specifically investigated BD,[11] while another[19] included a small subgroup of nine patients with bipolar depression alongside its primary MDD population. One study enrolled older adult inpatients with depression without an explicitly stated diagnostic framework.[21] The characteristics of each study and the patients included in each study (country, design, sample size, age, dose, treatment, intervention, and outcomes) are provided in Table 1.

We grouped the included trials into four subgroups based on the type of comparison to provide comparator-specific synthesis and subgroup analysis. The first subgroup encompassed studies in which ALC was administered as monotherapy and evaluated against placebo (n=8).[12,15–17,21,23,24,26] Of these, only four studies provided sufficient data for quantitative synthesis. The second subgroup comprised trials where ALC was given in combination with another antidepressant, compared with the same concomitant therapy, either with or without placebo (n=3).[19,20,22] A third subgroup consisted of head-to-head studies that compared ALC with another active pharmacological agent (n=2).[10,18] Finally, the fourth prespecified subgroup included trials in which ALC, when administered in combination with another active agent, was compared with placebo (n=2).[11,25] Subsequent results are presented within these comparator groups. These comparator categories were prespecified to keep comparisons clinically meaningful and to avoid pooling different control types that could blur ALC's added effect.

Risk of Bias Assessment

Risk of bias was assessed for all included studies. (Figure S1) Risk of bias was evaluated separately for efficacy and safety outcomes. Most randomized trials were rated as *low risk* or with *some concerns*, with very few domains rated as high risk. Among the RCTs, most domains were low risk, and concerns were mainly related to the randomization process and outcome measurement. One trial[14] had a high risk of bias for efficacy outcomes due to missing outcome data. We therefore conducted a sensitivity analysis excluding this trial from the primary meta-analysis. The crossover trial by Tempesta et al[21] was evaluated using the RoB 2 crossover tool, and judgments were consistent with other RCTs, showing *some concerns* in the randomization and measurement domains. The non-randomized trial by Pettegrew et al[12] assessed with ROBINS-I, showed a critical risk of bias from confounding and serious risk from participant selection, although other domains were low risk. Overall, this study was considered at serious to critical risk of bias, consistent with its open-label design.

Synthesis of Results

The primary meta-analysis pooled all RCTs across depression rating scales using standardized mean difference (SMD) random effects (REML). Secondary analyses were conducted by instrument (HDRS, BDI, MADRS).

Primary Meta-Analysis

Across 10 RCTs (n= 366 ALC; n= 359 control), the pooled estimate favored ALC (SMD −1.20, 95% CI −2.12 to −0.29; p = 0.01; Figure 2). While heterogeneity was high (I^2=96.86%), the direction of effect consistently favored ALC across robustness checks. In leave-one-out analyses, the pooled estimate remained in the same direction when omitting each

Table 1 Characteristics of the Included Studies and Patient Populations

Serial Number	Authors/ Year	Country	Design	Subjects (Diagnostic Criteria)	Sample Size (Total)	Participants				Age (Years)	Treatment Duration (Weeks)	ALC Dose (gm/ day)	Efficacy Results
						Treatment and Comparator Group (n)	Outcome Measures	Baseline	Endpoint				
1	Villardita et al 1983*	Italy	RCT	Depression (diagnostic system Not specified)	NA	ALC	NA	NA	NA	65-78	NA	1.5	• NA
						Placebo (28)							
2	Tempesta et al 1987	Italy	RCT (crossover design)	Hospitalized depressed elderly	24	ALC (12)	HDRS	64.5 ± 19.28	37 ± 7.67	>70	8 weeks	1	• HRSD scores significantly improved in almost all patients (P<0.01). • ALC showed better results in patients with more serious clinical symptoms (high baseline HAMD score) and significantly improved total scores in addition to depression, asthenia and somatization.
						Placebo (12)		57.18 ± 20.1	35.91 ± 9.64				
3	Nasca et al 1989*	United States	RCT	NA	NA	Mianserine + ALC in the first 20 days then ALC alone (10)	HDRS	NA	NA	55-75	5 weeks and 5 days	2	• No group difference was noted after 20 days, but ALC > PBO in HDS (P < 0.001) after 40 days. • HAMD scores: significantly reduced in ALC compared with placebo
						Placebo + Mianserine for 20 days then placebo alone (10)							
4	Bella et al 1990*	Italy	RCT	Dysthymic disturbances, DSM-III	60	Oral ALC solution (30)	HDRS	22	11	60-80	7 weeks and 4 days	3	• ALC > PBO in HRSD and BDI. ALC significantly reduced HRSD and BDI scores compared to control and T0 (P<0.0001) • Only HRSD significantly decreased in control group (P<0.0002).
							BDI	24	9				
						Placebo (30)	HDRS	21	20				
							BDI	22	24				
5	Garzya et al 1990	Italy	RCT	Depressive disturbances, DSM III-R	28	ALC tablet (14)	HDRS	22.14 ± 3.255	13.78 ± 5.977	70-80	8 weeks and 4 days	1.5	• ALC > PBO ALC: effective against non-organic depression in the elderly and significantly decreases HDRS and BDI scores (P<0.005)
							BDI	22.92 ± 4.73	13.21 ± 7.34				
						Placebo (14)	HDRS	19.71 ± 2.16	17.78 ± 4.80				
							BDI	21.14 ± 3.99	19.35 ± 5.56				
6	Fulgente et al 1990	Italy	RCT	Dysthymic disorder, DSM III-R	52	ALC oral tablet (26)	HDRS	24.8 ± 2.71	12.3 ± 4.56	70-80	8 weeks and 4 days	3	• ALC improves depressive symptoms in elderly patients. • HDRS scores significantly decreased in both groups (placebo p = 0.0039, ALC p < 0.0001) • Improvement in BDI scores was only in ALC group (p < 0.0001).
							BDI	32.8 ± 7.53	14.4 ± 9.68				
						Placebo (26)	HDRS	23.7 ± 2.82	22.2 ± 3.22				
							BDI	33.0 ± 6.1	33.8 ± 7.36				

https://doi.org/10.2147/NDT.S586506

7	Gecele et al 1991	Italy	RCT	Major depression in elderly, DSM III-R	28	ALC oral tablet (14)	HDRS	39 ± 1.5	28 ± 3 (Under 20 for 6 patients)	66-79 (71.3 ± 3.8)	5 weeks and 5 days	2	• ALC > PBO ALC reduced HDRS (P<0.001) and showed anti-depressant effects (6 out of 14 were in remission).
						Placebo (14)		34 ± 1	37 ± 3				
8	Cornelissen et al 1992*	Italy	RCT	Unipolar major depression, DSM III-R	28	ALC oral tablet (14)	HDRS	38.71 ± 7.6	28 ± 12.2	66-79	5 weeks and 5 days	2	• ALC > PBO (0.006<P<0.155)
						Placebo (14)		N/A	N/A				
9	Pettegrew et al 2002*	United States	Non-randomized open-label clinical trial	Major Depressive Disorder, DSM-IV	8	ALC oral tablets (2)	HDRS	17.5	1.5	80 and 70 (mean age of 6 controls 73.6± 3.6)	12 weeks	3	• ALC > PBO Significant reduction of HDRS scores in ALC group
						Placebo (6)		N/A	N/A				
10	Zanardi et al 2006	Italy	RCT	Dysthymic disorder, DSM-IV	193	ALC tablets (99)	HAMD-21	22 ± 2.58	12.02 ± 7.28	18-60 (Mean 45 ± 12)	11 weeks	1	• ALC=Amisulpride Both groups showed significant improvement in HAM-D21 and MADRS scores similarly; • ALC showed better tolerability.
							MADRS	23.5 ± 5.37	12.99 ± 9.29				
						Amisulpride (94)	HAMD-21	22 ± 2.54	11.23 ± 7.48				
							MADRS	23.7 ± 4.89	11.39 ± 9.21				
11	Bersani et al 2013	Italy	RCT	Dysthymic Disorder in elderly (without cognitive deficit), DSM-IV	80	ALC (41)	HAMD-21	24 ± 3.2	15 ± 6.7	65-93 (Mean 71. 74 ± 8.59)	6 weeks	3	• In HAM-D and BDI ALC= Fluoxetine. Faster onset of effect by 1 week and better tolerability in ALC group. • Both groups significantly improved in HAM-D21 (P<0.001), and BDI (P<0.001) and showed similar clinical progression.
							BDI	24	15				
						Fluoxetine (39)	HAMD-21	23 ± 5	17 ± 5				
							BDI	24	18.5				
12	Brennan et al 2013	United States	RCT	Bipolar disorder, DSM-IV	40	ALC capsule + Alpha-Lipoic Acid (20)	HAM-D	23.3 ± 3.5	17.8 ± 5.6	18-55 (mean 45.45 ± 15.7)	12 weeks	1 g/day; week 1 to 2 gr/day week 2 to 3 gr/day) (mean dose 2275 ± 750.6)	• ALC+ALA=PBO. • No significant amelioration in depressive symptoms compared to placebo (P>0.2).
							MADRS	26.9 ± 3.1	20.5 ± 7.2				
						Placebo (20)	HAM-D	22.1 ± 3.2	17.9 ± 5.9				
							MADRS	25.9 ± 3	20.9 ± 6.2				
13	Gavrilova et al 2015	Russia	RCT (open-label)	Recurrent depressive disorder or bipolar depression, DSM-IV and ICD-10	40	Venlafaxine, Agomelatine, Fluvoxamine, with ALC (20)	HAM-D17	23.01 ± 3.22	4.9 ± 2.36	60-79	8 weeks	1	• Combination therapy with the ALC proved to be more effective compared to monotherapy with antidepressants. • More rapid clinical response has been shown for depression, anxiety, apathy, and cognitive dysfunction.
						Venlafaxine, Agomelatine, Fluvoxamine (20)		22.55 ± 3.39	8.68 ± 3.6				

(*Continued*)

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Table 1 (Continued).

Serial Number	Authors/ Year	Country	Design	Subjects (Diagnostic Criteria)	Sample Size (Total)	Participants				Age (Years)	Treatment Duration (Weeks)	ALC Dose (gm/ day)	Efficacy Results
						Treatment and Comparator Group (n)	Outcome Measures	Baseline	Endpoint				
14	Ramezani et al 2022	Iran	RCT	Major depressive disorder in adults, DSM-V	60	ALC oral capsule + Sertraline (30)	BDI	29.80 ± 9.22	11.98 ± 7.50	19-57 (mean 37 ± 9.71)	6 weeks	1	• ALC=Sertraline. ALC group showed considerable decrease in BDI score • No significant difference in improvement or side effects with Sertraline group
						Sertraline + placebo (30)		30.63 ± 8.1	13.37 ± 5.9				
15	Rao et al 2024	India	RCT	Mild to severe depression, DSM-V	120	Rejiyana capsules (ALC +Agmatine) + standard of care (60)	HAM_D17	24.98 ± 2.11	13.7 ± 3.47	18-65	12 weeks	NA	• ALC + Agmatine in HAM-D17, MADRS > PBO. • ALC showed notable response to therapy and HAM-D17 ($P<0.05$), MADRS, scores and depression severity decreased significantly.
							MADRS	30.08 ± 3.88	8.83 ± 2.45				
						Standard of care (60)	HAM_D17	24.71 ± 2.56	16.05 ± 1.99				
							MADRS	30.28 ± 3.67	17.13 ± 2.4				

Notes: Atypical Antipsychotic: Used at low doses for antidepressant effects (e.g., amisulpride). *included in the review but not pooled in the meta-analysis due to incomplete data.
Abbreviations: ALC, Acetyl-L-Carnitine; BDI, Beck Depression Inventory; DSM, Diagnostic and Statistical Manual of Mental Disorders; HAM-D (HDRS), Hamilton Depression Rating Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; NA, not available, SSRI, Selective Serotonin Reuptake Inhibitor; SNRI, Serotonin-Norepinephrine Reuptake Inhibitor; TeCA, Tetracyclic Antidepressant; NaSSA, Noradrenergic and Specific Serotonergic Antidepressant.

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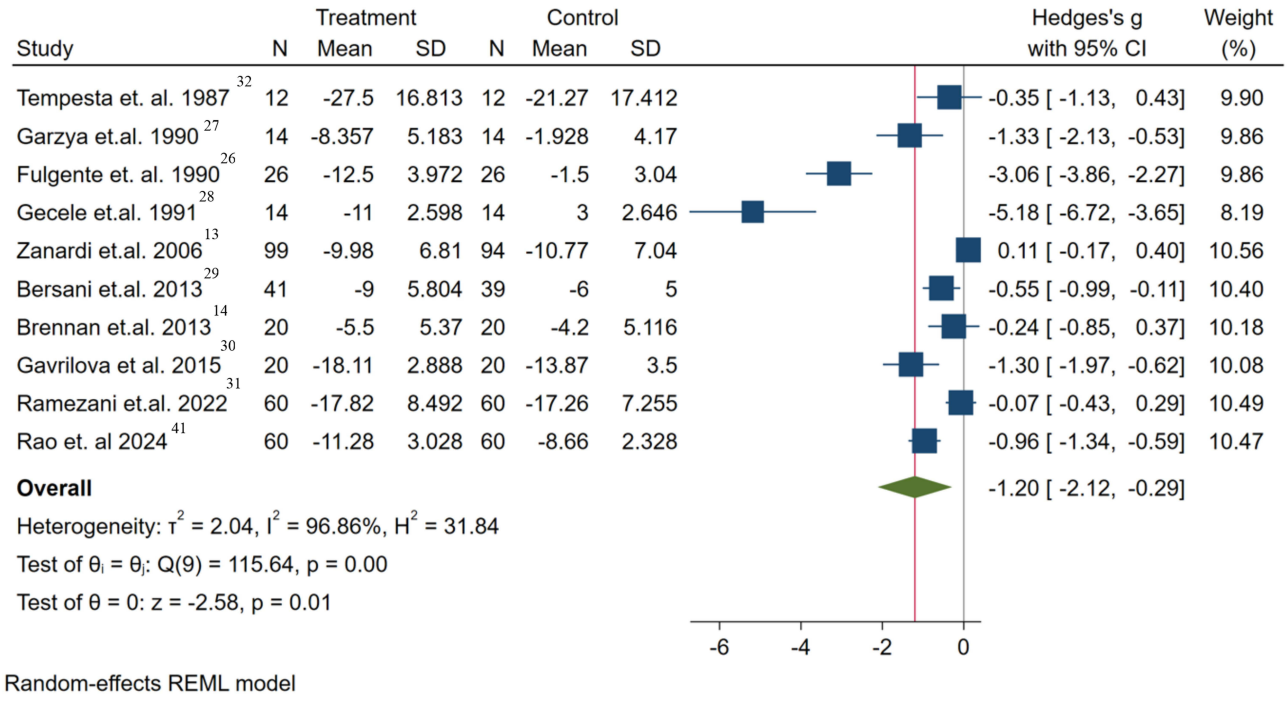


Figure 2 Forest plots showing the effects of acetyl-L-carnitine on depression severity scores measure.

study in turn (SMD range −1.36 to −0.82; all p≤0.03). Excluding the trial judged at high risk of bias for efficacy outcomes likewise did not materially change the estimate (SMD −1.32, 95% CI −2.33 to −0.31; p=0.01). Small-study effects were suggested by Egger's (p<0.001) and Begg's test (p=0.049); however, trim-and-fill imputed no missing studies, and the pooled estimate was unchanged (SMD −1.201, 95% CI −2.115 to −0.287). Taken together, these findings support a beneficial effect of ALC, although the magnitude of benefit likely varies across study settings and comparator types. In a sensitivity analysis restricted to placebo-controlled ALC monotherapy trials (4 studies), the pooled estimate also favored ALC (SMD −2.41, 95% CI −4.43 to −0.39; p=0.02) (Figure S3).

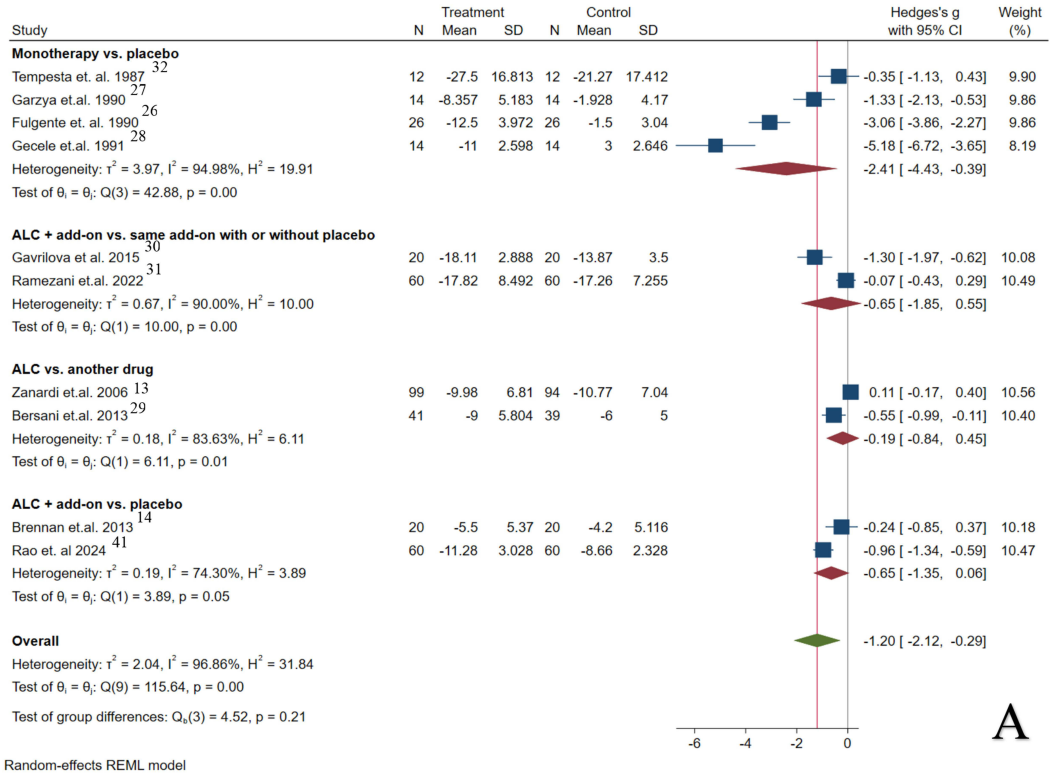
Subgroup Analysis

To explore potential sources of heterogeneity, we conducted prespecified subgroup analyses in the primary meta-analysis. Effects were stratified by comparator group using the four predefined categories, and by age groups: studies enrolling older samples ≥ 60 years vs primarily < 60 years. Because the number of trials within several strata was limited, these subgroup estimates and between-group comparisons should be interpreted cautiously.

In prespecified subgroup analyses of the pooled evidence, effects appeared more favorable in trials enrolling older adults (≥60 years; SMD −1.88, 95% CI −3.26 to −0.50) than in trials enrolling primarily younger adults (<60 years; SMD −0.28, 95% CI −0.77 to 0.20), with evidence of a between-group difference (p=0.03). When stratified by comparator groups, the pooled estimate was most favorable in monotherapy trials versus placebo (SMD −2.41, 95% CI −4.43 to −0.39), whereas the add-on designs versus the same background treatment (SMD −0.65, 95% CI −1.85 to 0.55), head-to-head comparisons versus another drug (SMD −0.19, 95% CI −0.84 to 0.45), and add-on designs versus placebo (SMD −0.65, 95% CI −1.35 to 0.06) showed more modest estimates and did not provide clear evidence of a between-group difference overall (p=0.21). Full estimates are demonstrated in Figure 3.

Meta-Regression

In exploratory random-effects (REML) meta-regression based on the primary pooled dataset, neither treatment duration nor ALC daily dose showed a clear association with the standardized treatment effect. For ALC daily dose, the



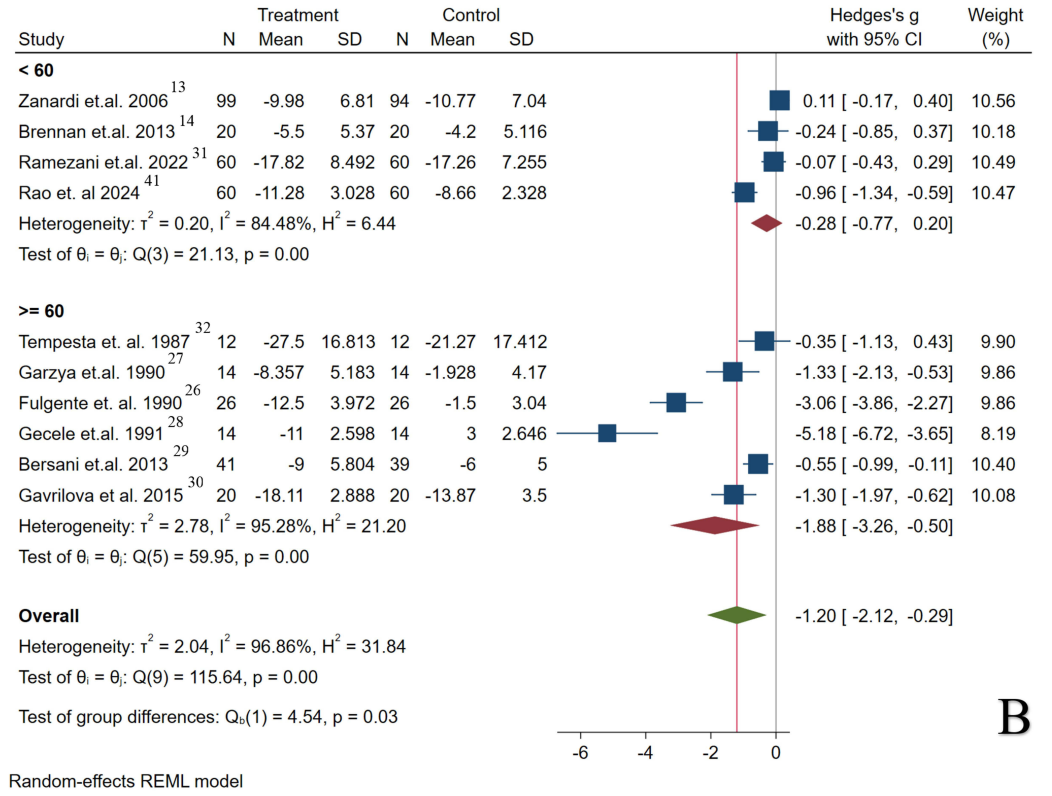


Figure 3 Subgroup analyses of the effects of acetyl-L-carnitine on depression severity scores, stratified by comparator type (**A**), and age group (**B**).

Table 2 Meta-Regression of Standardized Effect Sizes by Treatment Duration and Daily ALC Dose (Primary Pooled Analysis)

Moderator	k (Trials)	Coefficient	95% CI	P-value	R-Squared (%)
Treatment duration (weeks)	10	0.228	−0.154 to 0.609	0.242	0.00
ALC dose (g/day)	9	−0.722	−1.995 to 0.551	0.267	2.06

Note: Coefficients represent the change in standardized mean difference per 1-unit increase in the moderator.
Abbreviations: ALC, acetyl-L-carnitine; CI, confidence interval; k, number of trials.

coefficient was −0.72 SMD units per 1 g/day (95% CI −2.00 to 0.55; p=0.267). For treatment duration, the coefficient was 0.23 SMD units per additional week (95% CI −0.15 to 0.61; p=0.242). Full estimates are reported in Table 2.

Secondary Meta-Analysis

As secondary analyses stratified by depression rating scale, we synthesized depressive-symptom severity separately for the most frequently reported scales. On HDRS (9 trials; n=306 ALC, n=299 control), the pooled estimate favored ALC (SMD −1.38, 95% CI −2.41 to −0.34; I^2=96.9%; Figure S2A). On BDI (4 trials; n=141 ALC, n=139 control), the pooled estimate also favored ALC, though the confidence interval included the possibility of no effect (SMD −1.33, 95% CI −2.80 to 0.14; I^2=96.5%; Figure S2B). On MADRS (3 trials; n=179 ALC, n=174 control), the pooled estimate was similarly in the direction favoring ALC (SMD −0.81, 95% CI −2.42 to 0.81; I^2=97.5%; Figure S2C). Additional rating scale–specific diagnostics (eg., leave-one-out analyses and small-study effect assessments) are provided in the Supplement.

Five studies could not be included in the quantitative synthesis because they did not report depressive-symptom outcomes with the summary statistics needed to calculate the effect size. One trial[33] studied older adults over 40 days; during the first 20 days, participants received ALC plus Mianserine versus placebo plus Mianserine, followed by ALC alone versus placebo alone for the remaining 20 days, with no between-group difference at day 20 but greater improvement by day 40, favoring ALC on the Hamilton scale (p<0.001). A placebo-controlled trial[34] reported that ALC (3 g/day for 53 days) produced greater improvement than placebo on both the Hamilton scale and BDI (p<0.0001). Another placebo-controlled study[35] reported clinical improvement alongside circadian biomarker assessment, noting that seven participants had more than a 10-point decrease in DSM-III-R depression score after ALC treatment. Also, a small non-randomized study[15] in two older adults treated with ALC (2 g/day for 12 weeks), reported a decrease in HDRS scores from 15 to 0 and from 20 to 3 by week 12 and compared outcomes with six non-depressed controls. Finally, Villardita et al[36] evaluated ALC versus placebo, but did not report depressive-symptom efficacy results in a way that could be summarized quantitatively.

Adverse Events

Of the 15 trials, four did not report adverse event (AE) data.[17,19,22,26] Given incomplete and inconsistent reporting, AE findings were summarized descriptively. Where patient-level incidence was available, the proportion with ≥1 AE ranged from 0–35% in treatment arms and 10–46% in controls. In studies reporting event counts, ALC arm events were mainly categorized as gastrointestinal (GI) and central nervous system (CNS), with other systems (skin/subcutaneous, urinary, cardiovascular, endocrine/metabolic, reproductive) reported infrequently.

In the first subgroup (ALC vs placebo), three studies[15,21,23] reported no AEs in either arm, and one[16] found no between-group difference. Also, one study[12] reported only mild AEs with ALC (dry mouth, n=1; increased perspiration, n=1). In the second subgroup (ALC add-on vs the same background drug), Gavrilova et al[19] observed AEs in 35% with ALC add-on versus 45% with antidepressant alone, and Ramezani et al[20] reported AEs in three patients (1 in ALC + sertraline, 2 in sertraline + placebo). Both trials mainly reported CNS events, with no serious AEs. In direct comparisons of ALC with active drugs, ALC had fewer reported AEs, mostly CNS or GI, while comparator events reflected drug-specific profiles (eg., endocrine events with amisulpride). Finally, in the fourth subgroup (ALC combination vs placebo), GI events were most frequent in both arms, followed by CNS.[11,25]

Across the studies that reported serious/severe AEs, serious events were rare (2 in the treatment arm and 1 in the control) and, when adjudicated, not attributed to ALC.[10,11] Notably, no serious AEs occurred in add-on trial.[19] Severe AEs were reported in 1 ALC recipient and 3 controls on amisulpride.[10] Also, Bersani et al reported moderate-severe AEs in 3 fluoxetine-treated patients.[18] Overall, ALC was generally well tolerated, with predominantly mild GI and CNS events, and no evidence of excess serious AEs compared with controls. Full per-study counts, arm-level percentages, and system distributions are provided in S1.

Discussion

To the best of our knowledge, this is a latest systematic review and meta-analysis to examine the current evidence of ALC use in mood disorders especially MDD across RCTs and non-randomized trials as well.

Our study synthesized evidence based on 15 clinical trials of ALC for depressive disorders. By incorporating more recent trials and stratifying results by rating scales, comparator groups, age, and dose, the present study provides a more granular, clinically interpretable synthesis. Across rating scales, estimates generally favored ALC, with the clearest statistically significant effect on HDRS; on BDI and MADRS, effects favored ALC but varied among studies. Largest effects were observed in *monotherapy vs placebo/no treatment*, while *head-to-head* comparisons did *not demonstrate superiority* of ALC over antidepressant drugs. ALC was generally well tolerated, with predominantly mild gastrointestinal or central nervous system adverse events and no excess of serious harms compared with controls. These findings align with and extend earlier reviews suggesting antidepressant potential for ALC.[11]

Our findings indicate that, when used as a standalone treatment, ALC significantly reduced depressive symptoms compared to placebo or no treatment. Additionally, In the limited head-to-head trials available, ALC demonstrated comparable effectiveness to commonly used antidepressants, especially, Selective Serotonin Reuptake Inhibitor (SSRI), Serotonin-Norepinephrine Reuptake Inhibitor (SNRI), Tetracyclic Antidepressant (TeCA), Noradrenergic and Specific Serotonergic Antidepressant (NaSSA), Atypical Antipsychotics like Amisulpride used at low doses for antidepressant effects in this meta-analysis. Importantly, while the incidence of adverse effects was similar between ALC and placebo/no intervention, ALC was associated with a lower incidence of adverse effects compared to antidepressant medications.

ALC may exert antidepressant effects through several mechanisms. It promotes neuroplasticity in brain regions like the hippocampus by increasing BDNF levels, glutamate release, and upregulating mGLU2 receptors, particularly in the hippocampus and prefrontal cortex.[37] It may also correct metabolic imbalances, such as myo-inositol deficiency, which is linked to depression.[38] Additionally, ALC modulates neurotransmitters by increasing serotonin levels and enhancing dopamine and serotonin output in meso-cortico-limbic areas, potentially protecting against stress.[39] Meta-analyses also suggest ALC reduces pain—a common, often overlooked contributor to depression.[40]

Clinical Efficacy

Clinically, the pooled effect sizes suggest that ALC can provide meaningful benefits in reducing depressive symptoms. Stronger effects observed in older adult populations may reflect unique pathophysiological mechanisms of late-life depression, including mitochondrial dysfunction and neurodegenerative processes, which ALC could plausibly target.

Treatment effects of ALC appear context-dependent: the strongest benefit emerged in monotherapy vs placebo; effects were relatively similar in head-to-head comparisons, and small variations were noted in studies using ALC in combination and comparing it to the same drug. Larger effects in studies enrolling older samples (≥ 60 years) were observed, but the remaining between-study findings warrant prospective confirmation.

In exploratory random-effects (REML) meta-regression based on the primary pooled dataset, neither treatment duration nor ALC daily dose showed a clear association with the standardized treatment effect. Therefore, the available data do not allow firm conclusions about dose-response or duration-response relationships. Given the number of trials, we want to highlight that this meta-regression had limited power; therefore, these findings should not infer the absence of a dose–response or duration effect.

These findings suggest potential clinical roles for ALC in patient groups underserved by current antidepressant options, including those with poor tolerability to standard antidepressants or with late-onset depressive syndromes. Prior meta-analyses were limited by smaller evidence bases and less granular analyses of outcome measures. Unlike a prior

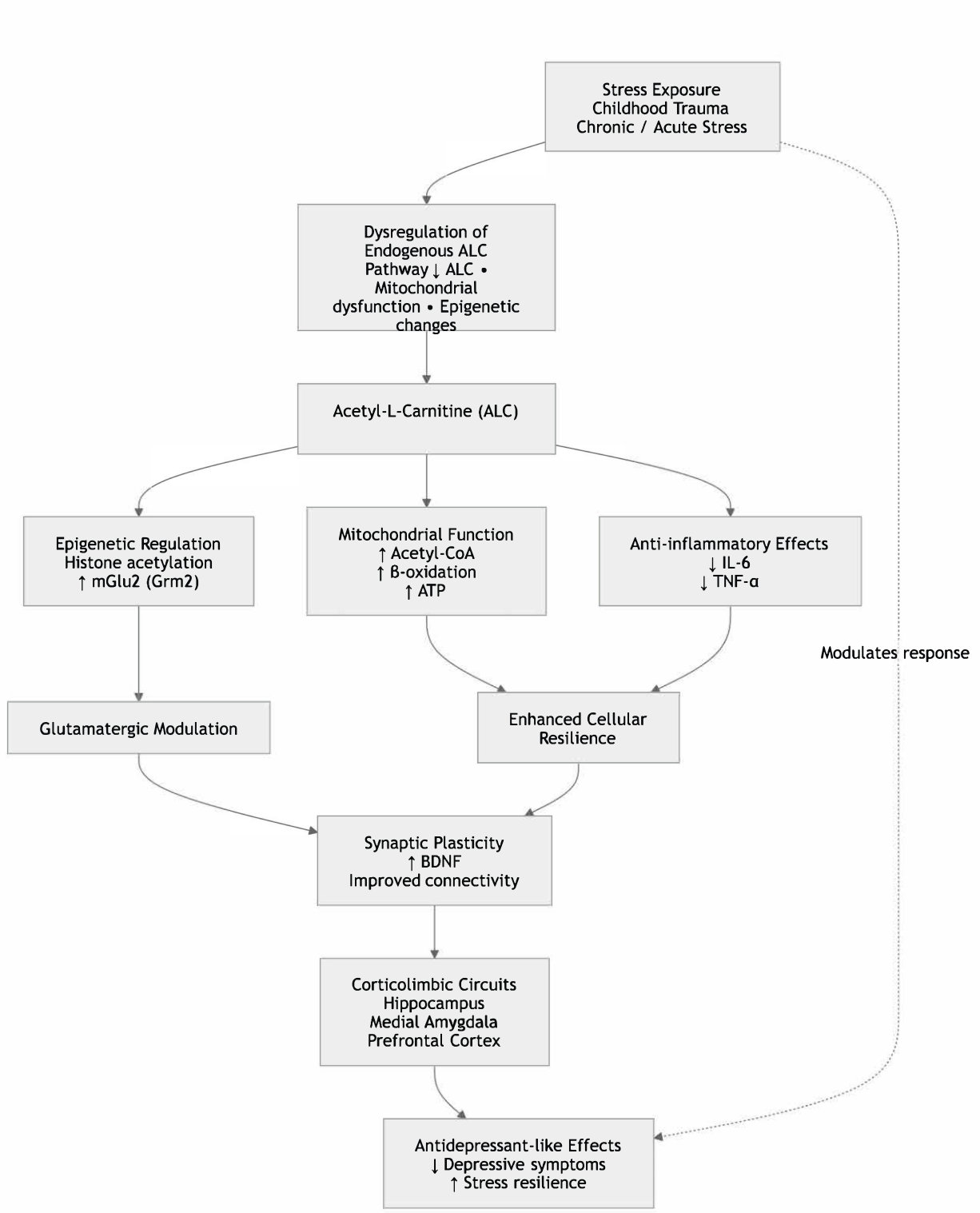


Figure 4 Proposed mechanistic model of acetyl-L-carnitine (ALC) in depression and stress-related modulation.

meta-analysis,[11] we modeled with HDRS, BDI, and MADRS separately rather than prioritizing a single scale. While the later emphasized a dose-response effect and found no role for follow-up, however, we observed no consistent dose gradient but did find that longer follow-up linked to greater improvement on self-reported symptoms (BDI only). Despite methodological differences, both reviews found ALC associated with greater improvement in depressive symptoms versus control.

Safety & Tolerability of ALC

Beyond efficacy, safety is a major consideration in the management of depression, particularly among older adults and those with comorbid conditions. Across included trials, ALC was well tolerated, with adverse events primarily mild and limited to gastrointestinal or central nervous system complaints. Serious adverse events were rare, and when occurred, they were not attributed to ALC. Compared with active comparators, ALC was associated with a more favorable adverse event profile, further supporting its potential role as a safer therapeutic option, especially for vulnerable populations.[41]

Our review has several methodological strengths. It represents the most comprehensive synthesis of randomized and controlled evidence for ALC to date, covering more than four decades of research. By analyzing results separately by rating scale, conducting prespecified subgroup and meta-regression analyses, and assessing robustness through sensitivity tests, this study provides a comprehensive evaluation of the evidence. Risk of bias was also systematically assessed using standard tools, adding further transparency to the interpretation of findings.

Nevertheless, the underlying evidence base has important limitations. In the current review, five eligible studies were excluded from quantitative synthesis due to incomplete/non-extractable data. Also, the previous literature dominated by older trials from specific regions (mostly Europe), which may limit generalizability to other settings. Additionally, high heterogeneity among studies was observed, reflecting the variability in study designs, populations, and assessment tools. Funnel plot asymmetry and Egger's tests suggested potential small-study effects in some datasets (HDRS, BDI), raising concerns about publication bias. Many studies had small sample sizes, and trial quality varied. Additional limitations were minimal BD data. Older literature with high risk of bias. Overall GRADE would probably be low with high risk of publication bias. Some studies have missing MDD diagnostic criteria. To enhance interpretability despite this variability, we pooled outcomes within instruments (HDRS, BDI, MADRS), conducted prespecified subgroup analyses by comparator group and age, used random-effects models, performed leave-one-out sensitivity analyses and publication-bias diagnostics, and applied meta-regression to examine treatment duration and daily dose.

Proposed Mechanistic Model of ALC in Depression and Stress-Related Modulation

ALC may exert antidepressant effects through converging mechanisms including mitochondrial bioenergetic enhancement, epigenetic upregulation of mGlu2 expression, and reduction of neuroinflammation. These processes enhance synaptic plasticity within corticolimbic circuits (hippocampus, medial amygdala, prefrontal cortex). Stress exposure, particularly early-life adversity, may dysregulate endogenous ALC signaling and moderate treatment response (Figure 4).

Conclusions

ALC shows promise as a novel treatment avenue for mood disorders, especially for depression in older adults, and for individuals with treatment resistance depression. Its diverse actions on neuroplasticity, neurotransmission, and mitochondrial function reinforce its therapeutic potential. Future research studies should prioritize large multicenter RCTs that apply standardized diagnostic criteria and validated depression rating scales. Further investigation of dose–response effects and long-term outcomes is needed to clarify the durability and clinical significance of ALC's benefits.

Author Contributions

Study concept and design: Kumar, Pagali, Singh. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Kumar and All authors. Statistical analysis: Pagali and Hasset. Obtained funding: NA.Critical revision of

the manuscript for important intellectual content: All authors. Administrative, technical, or material support: Kumar. Study supervision: Pagali. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

Dr. Pagali has received the Mayo Clinic CTSA (Mayo Clinic Small grants) through grant number UL1TR002377 from the National Center for Advancing Translational Sciences (NCATS), a component of the National Institutes of Health (NIH). Dr. Croarkin reported serving on the advisory board for MindMed; receiving equipment support grant in kind for federally funded study from MagVenture Inc and Neuronetics Inc; receiving grants from Innosphere Inc; and receiving payment for editorial work from Journal of Child and Adolescent Psychopharmacology outside the submitted work. Dr. Singh has received research grant support from Mayo Clinic, the National Network of Depression Centers (NNDC), and Breakthrough Discoveries for Thriving with Bipolar Disorder (BD2). He is a KL2 Mentored Career Development Program scholar, supported by CTSA Grant Number KL2TR002379 from the National Center for Advancing Translational Science (NCATS). Dr. Singh has received honoraria (to Mayo Clinic) from Elsevier for editing a Clinical Overview on Treatment-Resistant Depression. Dr. Frye received grant support from Assurex Health, Baszucki Group, Myriad, Mayo Foundation and BD2, received CME travel and honoraria from Carnot Laboratories and American Physician Institute and has Financial Interest/Stock ownership/Royalties from Chymia LLC. The funding sources had no influence on the study results, data interpretation, or decision to submit for publication. The remaining authors report no potential competing interests in this work.

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