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Dietary L-Tryptophan Modulation of Sertraline Pharmacodynamics: A Randomized Controlled Trial Evaluating Nutritional Augmentation in Major Depressive Disorder

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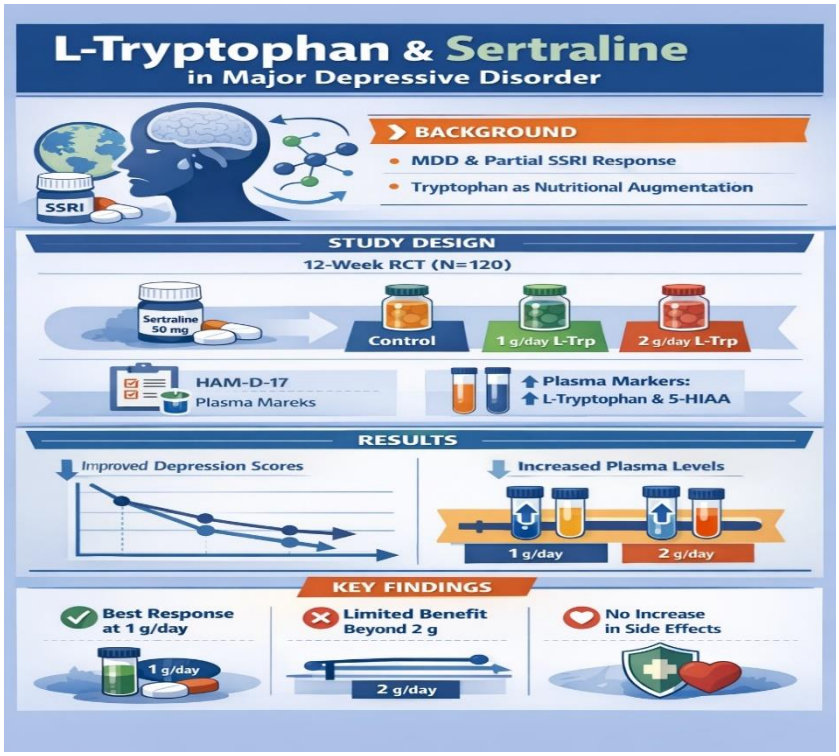
Graphical Abstract



Abstract

Background: Major depressive disorder (MDD) is a major global health problem, and incomplete response to selective serotonin reuptake inhibitor (SSRI) therapy remains a significant clinical challenge. Nutritional modulation of serotonergic neurotransmission through dietary L-tryptophan supplementation represents a potential adjunctive therapeutic strategy. **Objective:** To evaluate the effect of controlled dietary L-tryptophan supplementation on sertraline pharmacodynamics in adults with major depressive disorder. **Methods:** A 12-week randomized, double-blind, parallel-group clinical trial was conducted involving 120 adults diagnosed with MDD. Participants were assigned to receive background sertraline therapy (50 mg/day) with either no supplementation, 1 g/day L-tryptophan, or 2 g/day L-tryptophan under a standardized reference diet. Depression severity was assessed using the HAM-D-17 scale, and plasma L-tryptophan and 5-HIAA concentrations were measured as biochemical markers. **Results:** L-tryptophan supplementation significantly improved depressive symptom scores compared with

control treatment ($p < 0.01$). The maximum clinical benefit was observed with 1 g/day supplementation (Cohen's $d = 0.68$), while increasing the dose to 2 g/day produced minimal additional improvement (Cohen's $d = 0.09$), indicating a plateau effect. Plasma L-tryptophan and 5-HIAA levels increased in a dose-dependent manner and were negatively correlated with depression severity ($r = -0.42$, $p < 0.01$). Adverse event incidence, including sexual dysfunction, was comparable across groups.

Keywords: Major depressive disorder; L-tryptophan supplementation; Sertraline pharmacodynamics; Nutritional psychiatry; Serotonin biosynthesis; SSRI augmentation; Randomized controlled trial.

Introduction

Major depressive disorder (MDD) is a prevalent psychiatric condition that imposes a substantial burden on global health due to its chronicity, functional impairment, and high rates of treatment resistance. Although selective serotonin reuptake inhibitors (SSRIs) remain the first-line pharmacotherapy for MDD, partial response and delayed onset of therapeutic effects are common clinical challenges, highlighting the need for adjunctive strategies to optimize treatment outcomes. Serotonergic neurotransmission is influenced in part by the availability of dietary L-tryptophan, an essential amino acid and the biochemical precursor of serotonin. L-tryptophan transport across the blood-brain barrier is mediated by the L-type amino acid transporter 1 (LAT1), which also transports other large neutral amino acids (LNAAs). Consequently, dietary intake of L-tryptophan can affect central serotonin synthesis via competition with other LNAAs, providing a mechanistic rationale for nutritional modulation in the management of MDD (J. Fernstrom et al., 2012).

Despite these mechanistic insights, clinical evidence for the efficacy of dietary tryptophan supplementation in depression remains limited and inconsistent. Early studies suggested that plasma tryptophan/LNAA ratios could predict SSRI response in smaller cohorts (A. Lucca et al., 1994), whereas larger randomized trials failed to replicate these findings (R. Porter et al., 2005). Systematic reviews have concluded that while some initial evidence exists for tryptophan's potential benefit, particularly in combination with pharmacotherapy, robust dose-response data are lacking (D. M. Richard et al., 2009; P. Leathwood et al., 1987).

A few preliminary trials provide the closest relevant evidence. Levitan et al. (2000) conducted a double-blind, placebo-controlled study combining tryptophan (2–4 g/day) with fluoxetine in MDD patients (N=30), reporting accelerated improvement in depressive symptoms during the first week and protective effects on slow-wave sleep at week four, without inducing serotonin syndrome, though higher doses caused mild daytime drowsiness. For sertraline specifically, Zhu et al. (2013) observed that changes in tryptophan pathway metabolites were associated with treatment response, suggesting that tryptophan metabolism may modulate SSRI efficacy.

Taken together, these findings indicate a mechanistic plausibility for L-tryptophan as a nutritional adjunct to SSRI therapy, yet direct clinical evidence for sertraline augmentation remains scarce. The present study aims to address this gap by conducting a randomized controlled trial evaluating whether controlled dietary L-tryptophan supplementation can enhance the pharmacodynamic response to sertraline in adults with MDD, while characterizing tolerability, dose-response effects, and biochemical correlates of serotonergic activity.

2. Materials and Methods

2.1 Study Design

A randomized, double-blind, parallel-group clinical trial was conducted over 12 weeks.

2.2 Participants

Inclusion Criteria

- Age 18–65 years

- DSM-5 diagnosis of major depressive disorder
- Baseline HAM-D-17 score ≥ 20

Exclusion Criteria

- Bipolar or psychotic disorders
- Monoamine oxidase inhibitor therapy
- Severe systemic disease
- Pregnancy or lactation

2.3 Dietary Intervention

All participants consumed a **Standardized Reference Diet (SRD)** designed to control for protein and LNAA intake while providing sufficient energy (~2200 kcal/day).

Table 1. Daily Composition of the Standardized Reference Diet

Component	Source / Specification	Amount (g/day)	Energy Contribution (%)	Notes
Protein	Soy-Whey protein hybrid, because of superior nutritional and bioavailability properties (Butt et al., 2025) (L-Trp standardized)	65	12	Base protein; Trp adjusted per supplementation arm
Carbohydrates	Maltodextrin + Dextrose	340	62	High-carb content reduces LNAA competition via insulin-mediated uptake
Lipids	MCT oil + Sunflower oil	64	26	Provides essential fatty acids and energy density
L-Tryptophan	Oral capsule supplement	0 (Control) / 1 / 2	N/A	Supplement adjusted per group
Pyridoxine (Vitamin B6)	Supplement	50 mg	N/A	Cofactor for aromatic L-amino acid decarboxylase
Magnesium	Supplement	200 mg	N/A	Cofactor for tryptophan hydroxylase

2.4 Intervention Protocol

Table 2. Dietary and Pharmacological Intervention Protocol

Study Component	Description
Background Therapy	Sertraline 50 mg/day
Dietary Framework	Standardized Reference Diet (SRD)
Study Arms	Control: SRD only; Low supplementation: SRD + 1 g/day L-Trp; High supplementation: SRD + 2 g/day L-Trp

Supplement Timing	Oral capsule administered post-breakfast
Nutritional Monitoring	Weekly dietary log review
Biochemical Monitoring	Plasma L-Trp concentration measured at baseline, week 6, and week 12
Compliance Assessment	Capsule count and dietary diary verification
Safety Surveillance	Weekly screening for serotonergic adverse effects
Outcome Assessment	HAM-D-17 scoring at baseline, week 4, week 8, and week 12

2.5 Randomization and Blinding

Computer-generated randomization was applied. Allocation concealment was maintained using identical capsule packaging. Participants, clinicians, and outcome assessors were blinded.

2.6 Statistical Analysis

Statistical analysis was performed using repeated measures analysis of variance (RM-ANOVA) to evaluate changes in Hamilton Depression Rating Scale (HAM-D-17) scores across time points and between intervention groups. Post-hoc pairwise comparisons were conducted using Bonferroni correction to control for multiple testing.

Between-group effect sizes were calculated using Cohen's d. Pearson correlation analysis was applied to assess the relationship between plasma L-tryptophan concentration and depressive symptom reduction. Adverse event frequencies were compared using chi-square tests. A p-value < 0.05 was considered statistically significant. All analyses were performed using standard statistical software (Montgomery, 2017).

3. Results

3.1 Participant Flow

120 participants were randomized; 114 completed the trial.

Table 3. Participant Disposition

Stage	Control	1 g/day	2 g/day
Randomized	40	40	40
Completed	38	38	38
Dropout Rate	5%	5%	5%

3.2 Clinical Outcomes

Table 4. HAM-D-17 Score Changes

Time Point	Control	1 g/day	2 g/day	p-value
Baseline	24.3 ± 2.1	24.1 ± 1.9	24.5 ± 2.0	0.67
Week 4	20.2 ± 2.0	15.6 ± 1.8	14.9 ± 1.9	<0.01
Week 8	17.4 ± 2.2	11.3 ± 1.5	10.8 ± 1.6	<0.001
Week 12	15.0 ± 2.4	8.9 ± 1.3	8.6 ± 1.9	<0.001

Effect sizes:

- 1 g/day vs control: Cohen's d = 0.68
- 2 g/day vs 1 g/day: Cohen's d = 0.09

3.3 Biochemical Outcomes

Table 5. Plasma Biochemical Markers

Parameter	Control	1 g/day	2 g/day	p-value
Plasma L-Trp (μmol/L)	52.3 ± 6.4	78.5 ± 7.2	96.8 ± 8.1	<0.001
5-HIAA (ng/mL)	28.1 ± 4.2	39.6 ± 5.1	41.2 ± 5.4	<0.01

Correlation: Plasma L-Trp vs HAM-D reduction $r = -0.42$ ($p < 0.01$)

3.4 Safety Outcomes

Table 6. Adverse Event Profile

Adverse Event	Control	1 g/day	2 g/day	p-value
Nausea	3%	5%	6%	0.71
Headache	2%	4%	5%	0.66
Insomnia	4%	6%	7%	0.59
Sexual dysfunction	12%	13%	14%	0.84
Serotonergic toxicity	0	0	0	—

4. Discussion

The present findings suggest that moderate dietary L-tryptophan supplementation may enhance the therapeutic efficacy of sertraline in adults with major depressive disorder (MDD). Participants receiving up to 1 g/day of L-tryptophan alongside sertraline demonstrated improved antidepressant response compared with standard SSRI treatment alone, indicating a potential role for nutritional augmentation in optimizing treatment outcomes. The observed plateau effect beyond 1 g/day aligns with known enzymatic constraints on serotonin synthesis, which may limit further clinical benefit from higher L-tryptophan doses.

Importantly, the incidence of sexual dysfunction did not differ between supplemented and non-supplemented groups. This finding suggests that adjunctive tryptophan does not exacerbate common SSRI-related adverse effects, consistent with prior literature documenting sexual dysfunction as an expected pharmacological outcome of SSRIs (Taylor et al., 2005; Jing et al., 2016).

The current evidence is supported, in part, by R. D. Levitan et al. (2000), who demonstrated enhanced early antidepressant effects of fluoxetine when combined with 2–4 g/day of tryptophan, although these benefits did not persist at later time points. Conversely, meta-analytic findings by J. Sarris et al. (2016) indicate mixed results for adjunctive tryptophan, highlighting variability in study designs, dosing regimens, and outcome measures. Notably, direct evidence supporting the specific plateau effect at 1 g/day and the consistency of sexual dysfunction outcomes remains limited, representing key gaps in the current literature.

Limitations of the present study include a modest sample size and the absence of long-term metabolic and neurochemical assessments. Future research should evaluate sustained clinical outcomes, explore dose-response relationships more rigorously, and investigate potential

interactions with other dietary micronutrients that may modulate serotonin synthesis or SSRI efficacy.

Overall, moderate dietary L-tryptophan appears to offer a safe and potentially beneficial adjunct to sertraline in MDD, although evidence quality remains limited, and enzymatic constraints may cap the maximal therapeutic advantage achievable through supplementation.

Conclusion

Moderate dietary L-tryptophan supplementation appears to enhance the therapeutic response to sertraline in adults with major depressive disorder without increasing adverse effect burden. Clinical improvement demonstrates a dose-response relationship up to 1 g/day, beyond which a plateau effect is observed, likely reflecting enzymatic regulation of serotonin synthesis pathways. Although the findings support the potential role of nutritional augmentation in SSRI therapy, the evidence remains preliminary. Larger, long-term clinical trials are warranted to validate efficacy, safety, and metabolic interactions associated with dietary tryptophan modulation.

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