Original Article

Efficacy and Safety of Acetyl-L-Carnitine and Agmatine Sulfate Compared to Escitalopram in Major Depressive Disorder: A Double-Blind Study

G. Prasad Rao[1], Chyanya Deepak P[2], Simhachalam Gurugubel[3], Avsarala Uma Devi[4], Mounika Gongareddy[5], Yashaswini Akoju[6]

[1]Consultant Neuro-Psychiatrist, Asha Hospital Hyderabad, [2]Consultant Psychiatrist, Asha Hospital Hyderabad, [3]Consultant Physician, Asha Hospital Hyderabad, [4]Research Scholar, Asha Hospital Hyderabad, [5]Research Assistant, Asha Hospital Hyderabad, [6]Research Assistant, Asha Hospital Hyderabad.

How to cite this article: G. Prasad Rao, Chyanya Deepak P, Simhachalam Gurugubel et. al. Efficacy and Safety of Acetyl-L-Carnitine and Agmatine Sulfate Compared to Escitalopram in Major Depressive Disorder: A Double-Blind Study. Indian Journal of Public Health Research and Development / Vol. 16 No. 4, October-December 2025.

Abstract

Background: To evaluate the efficacy and safety of fixed dose combination (FDC) containing Acetyl-L-carnitine and Agmatine Sulfate versus Escitalopram in treating Major Depressive Disorder (MDD).

Methods: Sixty participants, aged 18-65, diagnosed with MDD, were randomized to receive either Fixed dose containing (FDC) containing Acetyl-L-carnitine and Agmatine Sulfate or Escitalopram for 28 days. Depression severity was measured using the Hamilton Rating Scale for Depression (HAM-D17) and Montgomery-Asberg Depression Rating Scale (MADRS). Safety was assessed by monitoring adverse events and vital signs. FDC containing Acetyl-L-carnitine and Agmatine Sulfate significantly reduced HAM-D17 and MADRS scores more than Escitalopram (mean changes: -8.67 vs. -3.80 and -12.33 vs. -9.66, respectively). Adverse events were fewer in the FDC containing Acetyl-L-carnitine and Agmatine Sulfate group, with only one reported case compared to seven in the Escitalopram group.

Conclusion: FDC containing Acetyl-L-carnitine and Agmatine Sulfate demonstrated superior efficacy and a better safety profile compared to Escitalopram, suggesting it as a promising alternative treatment for MDD. Further research is needed to confirm long-term benefits and optimal dosing.

Key words: MDD, Acetyl-L-carnitine, Agmatine Sulfate, Escitalopram, Depression.

Introduction

Major Depressive Disorder (MDD) is a mental health disorder characterized a persistently low or depressed mood and also loss of interest in enjoyable activities. Other symptoms are persistent fatigue, significant changes in appetite or weight and

Corresponding Author: G. Prasad Rao, Consultant Neuro-Psychiatrist, Director of Division of Schizophrenia & Psychopharmacology, Asha Hospitalroad no 14 Banjara hills Hyderabad India Telangana.

E-mail: prasad40@gmail.com

Submission date: November 4, 2024 **Revision date:** Febuary 19, 2025 **Published date: September 24, 2025**

sleep disturbances. MDD also presents emotional challenges such as excessive guilt and a lack of drive, alongside cognitive impairments.[1]

Approximately 300 million people worldwide are getting affected by MDD, with increasing prevalence across all age groups, including pregnant women, the elderly, and children.[2-3]Globally, an estimated 5% of adults suffer from depression in any given year. In India, a recent study found that the overall weighted prevalence of depression is 8.6%, indicating a higher burden compared to the global average. Furthermore, among the estimated 29.6 million middle-aged and older adults affected by depression across the country, approximately 29.1 million remain untreated, highlighting a significant gap in mental health care.[4-5]

Clinical manifestations are consistent with those defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5): persistent depressed mood, reduced interest in daily activities, and an increased risk of suicide.[6-7]

Although Major Depressive Disorder (MDD) is common and associated with substantial psychological and socio-economic burden, treatment is limited by its heterogeneity and relatively poor response rates to standard antidepressants (SSRIs in particular). SSRIs, such as Escitalopram, are prescribed extensively; however, a high percentage of patients do not experience remission from all symptoms, and many will experience negative side effects. These challenges call for innovative therapeutic strategies with improved efficacy and safety profiles.

Acetyl-L-carnitine (ALC) as well as Agmatine Sulfate are novel candidates for the treatment of MDD. ALC supports mitochondrial energy production and exhibits neuroprotective and antidepressant-like effects by enhancing neuroplasticity and regulating neurotransmitters. Clinical research suggests that ALC is able to address depressive symptoms within a short time span through epigenetic effects and affect quality of life in a positive manner. [10-11] Agmatine, a polyamine derived from arginine, interacts with serotonin and glutamate systems, leading to modulation of inflammatory pathways and gut microbiota which have fast and long-term antidepressant effects.[12-13]

The present study assesses the effectiveness and safety of a fixed-dose combination (FDC) of Acetyl-L-carnitine and Agmatine Sulfate in MDD. The primary objective is to compare the reduction in depressive symptoms achieved by this combination to that of Escitalopram over 28 days. The secondary objective is to assess the safety and overall effectiveness of this FDC treatment, aiming to provide an alternative therapeutic option with synergistic benefits for patients with MDD.

Material and Methods

This is a double-blind, randomized, controlled trial was designed to assess the efficacy and safety of FDC of Acetyl-L-carnitine (500mg) and Agmatine Sulfate (250 mg) compared to Escitalopram (10 mg) in patients with Major Depressive Disorder (MDD). The study was conducted at a single center and included a total of 60 participants, both male and female, aged between 18 and 65 years. The study duration was 38 days, including a 3-day screening period, 28 days of treatment, and a 7-day follow-up period.

IMP Procurement, blinding and supply

The IMPs used in this study were procured from the market. A fixed-dose combination of Acetyl-L-carnitine and Agmatine Sulfate was manufactured by Celagenex Research (India) Pvt. Ltd. under the brand name Rejiyana®, while Escitalopram was manufactured by Sun Pharmaceutical Industries Ltd under the brand name of Nexito.

To maintain blinding, an unblinded pharmacist handled the repackaging and relabelling of the IMPs. As this was a double-blind study, the repackaged and relabelled study drugs were then shipped to the clinical site, ensuring that the blind was preserved throughout the study.

Participants were randomly assigned to one of two groups: Group A received FDC of Acetyl-L-carnitine and Agmatine Sulfate while Group B received Escitalopram. Both the participants and the study personnel were blinded to the treatment assignments to minimize bias.

Study Procedure and Assessments

The inclusion criteria for the study were participants with a HAM-D score of 18 and above,

those suffering from mild to severe depression, aged 18-65 years, and willing to provide signed informed consent. Additionally, participants with stable comorbid conditions such as diabetes or hypertension, receiving standard treatment for at least six months, were included. Exclusion criteria were patients with bipolar affective disorder, any form of schizophrenia, tuberculosis, or sarcoidosis, pregnant or lactating women, known allergies or intolerances to the study medication, women of childbearing potential not willing to use effective contraception, patients with high suicidal risk (MADRS >3), and those with significant medical disorders like hepatic insufficiency, uncontrolled diabetes, or renal impairment.

Primary outcomes were measured using the HAM-D17 and MADRS at baseline and at the end of the treatment period (Day 28). Secondary outcomes, including CGI scores and adverse events, were monitored throughout the study duration. Socio-demographic factors, known side effects of the experimental drug, severe adverse events, use of dietary supplements, and a full medication list were recorded at baseline and follow-up visits. Treatment adherence was assessed by counting the number of returned medication bottles at Day 28.

Data was analyzed using standard statistical methods. The efficacy of the treatment was evaluated by comparing the mean changes in HAM-D17 and MADRS scores from baseline to the end of the treatment period between the two groups. Secondary outcomes, such as CGI scores and the incidence of adverse events, were analyzed descriptively. This rigorous methodology ensures the reliability and validity of the study results, providing critical insights into the potential benefits of FDC of Acetyl-L-carnitine and Agmatine Sulfateas a novel treatment for Major Depressive Disorder.

Results and Discussion

The study included 60 participants, divided equally between the FDC of Acetyl-L-carnitine and Agmatine Sulfate group and the Escitalopram group, each consisting of 30 participants. All enrolled participants were Asian with mean age of 40.27 (FDC of Acetyl-L-carnitine and Agmatine Sulfate) and 37.2 years (Escitalopram). The gender distribution was relatively balanced, with 31 males (51.67%) and 29 females (48.33%).*(see figure 1)*

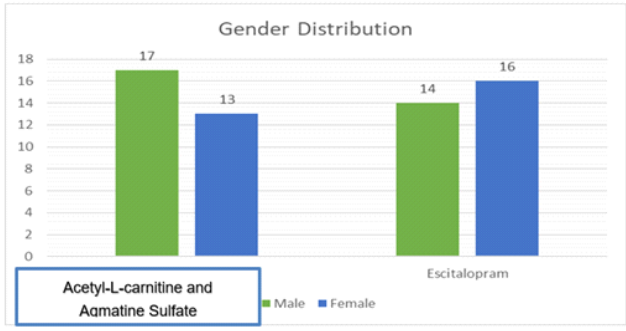

Figure 1: Gender distribution of the participants in each group

Vital signs of participants

The vital signs of participants were monitored at the start (Day 0) and the end (Day 28) of the study. In the Acetyl-L-carnitine and Agmatine Sulphate group, the mean pulse rate increased slightly from 80.83 to 81.96 beats per minute. Similarly, in the Escitalopram group, the pulse rate increased from 81.36 to 82.75 beats per minute.

For body temperature, the Acetyl-L-carnitine and Agmatine Sulfate group showed a slight increase from 97.46°F to 97.53°F, while the Escitalopram group remained relatively stable, changing from 97.44°F to 97.46°F.

The respiratory rate for Acetyl-L-carnitine and Agmatine Sulfate group increased marginally from 16.7 to 16.81 breaths per minute, whereas the Escitalopram group showed a slight decrease from 16.93 to 16.67 breaths per minute.

Seated systolic blood pressure in the Acetyl-L-carnitine and Agmatine Sulfate group rose slightly from 117.16 mmHg to 117.51 mmHg, and in the Escitalopram group, it increased from 117.2 mmHg to 117.64 mmHg. Finally, seated diastolic blood pressure in the Acetyl-L-carnitine and Agmatine Sulfate group increased from 79.83 mmHg to 80.37 mmHg, and in the Escitalopram group, it rose from 78.96 mmHg to 80.21 mmHg. Overall, the vital signs remained stable across both treatment groups, indicating that both treatments were well-tolerated with no significant adverse impacts on these parameters.*(see Table 1)*

Table 1: Vital Signs of Participants at Day 0 and Day 28

	Acetyl-L-carnitine and Agmatine Sulfate		Escitalopram	
	Day 0	Day 28	Day 0	Day 28
	(N=30)	(N=27)	(N=30)	(N=28)
Pulse Rate (Beats/Min)				
Mean (SD)	80.83 (3.86)	81.96 (4.27)	81.36 (3.25)	82.75 (3.32)
Median	81	82	82	83
Min, Max	70, 89	71, 89	73, 85	74, 88
Body Temperature (°F)				
Mean (SD)	97.46 (0.24)	97.53 (0.24)	97.44 (0.22)	97.46 (0.19)
Median	97.4	97.6	97.4	97.5
Min, Max	96.9, 98	97.1, 97.9	97, 97.9	97.1, 97.9
Respiratory Rate (Breaths/Min)				
Mean (SD)	16.7 (1.08)	16.81 (1.07)	16.93 (0.90)	16.67 (1.09)
Median	17	17	17	17
Min, Max	15, 18	15, 18	15, 18	15, 18
Seated Systolic Blood Pressure (mmHg)				
Mean (SD)	117.16 (5.45)	117.51 (5.48)	117.2 (5.16)	117.64 (5.02)
Median	119	118	120	119.5
Min, Max	110, 126	110, 127	110, 124	110, 125
Seated Diastolic Blood Pressure (mmHg)				
Mean (SD)	79.83 (2.52)	80.37 (1.94)	78.96 (2.79)	80.21 (3.25)
Median	80	80	80	80.5
Min, Max	72, 88	76, 84	70, 82	70, 88

Efficacy Outcomes

Hamilton Rating Scale for Depression (HAM-D17)

At baseline (Day 0), the mean HAM-D17 score for the Acetyl-L-carnitine and Agmatine Sulfate group was 20.46 (SD 1.94), which decreased to 11.79 (SD 3.29) on Day 28, reflecting a mean change of -8.67 (SD 1.35). The p-value for this change was 0.00, indicating statistical significance. In the Escitalopram group, the mean HAM-D17 score was 19.93 (SD 1.01) at baseline, which decreased to 16.13 (SD 3.00) on Day 28, resulting in a mean change of -3.80 (SD 1.98) with a p-value of 0.00.*(see Table 2)*

Table 2: Sum of the Hamilton Rating Scale for Depression (17-items) (HAM-D17)at Day 0 and Day 28

	Day 0	Day 28	Change from day 0
Acetyl-L-carnitine and Agmatine Sulfate			
Mean (SD)	20.46 (1.94)	11.79 (3.29)	-8.67 (1.35)
Median	20	12	-
Min, Max	18, 25	6, 18	-12, -7
p value	-	-	0.00
Escitalopram			
Mean (SD)	19.93 (1.01)	16.13 (3.00)	-3.80 (1.98)
Median	20	16	-
Min, Max	18, 22	11, 21	-7, -1
p value	-	-	0.00

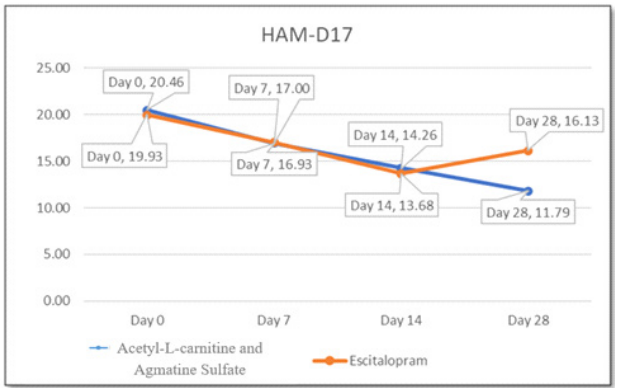

Figure 2: Sum of the Hamilton Rating Scale for Depression (17-items) (HAM-D17)at Day 0 and Day 28

Figure 2 shows sum of the Hamilton Rating Scale for Depression (17-items) (HAM-D17). The line graph shows that the decrease is is statistically significant in both group but REJIYANA® provided more favorable outcomes compared to Escitalopram.

Montgomery-Asberg Depression Rating Scale (MADRS)

For the Acetyl-L-carnitine and Agmatine Sulfate group, the baseline MADRS score was 30.70 (SD 4.38), which decreased to 18.36 (SD 4.87) on Day 28, showing a mean change of -12.33 (SD 0.49) with a p-value of 0.000. In the Escitalopram group, the baseline MADRS score was 30.43 (SD 4.09), which decreased to 20.76 (SD 5.56) on Day 28, resulting in a mean change of -9.66 (SD 1.46) with a p-value of 0.000.*(see Table 3)*

Table 3: Sum of Montgomery-Asberg Depression Rating Scale at Day 0 and Day 28

	Day 0	Day 28	Change from day 0
Acetyl-L-carnitine and Agmatine Sulfate			
Mean (SD)	30.70 (4.38)	18.36 (4.87)	-12.33 (0.49)
Median	30	19	-
Min, Max	24, 40	0, 24	-24, -16
p value	-	-	0.000
Escitalopram			
Mean (SD)	30.43 (4.09)	20.76 (5.56)	-9.66 (1.46)
Median	30	19.5	-
Min, Max	23, 38	11, 35	-12, -3
p value	-	-	0.000

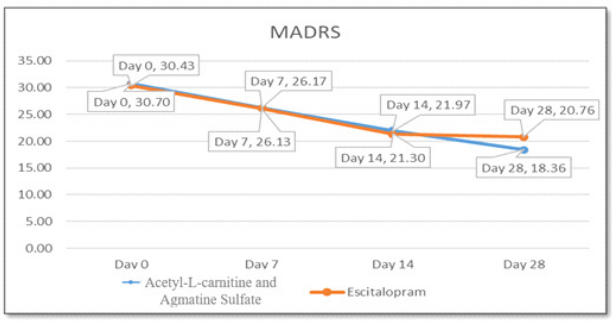

Figure 3: Sum of the Montgomery-Asberg Depression Rating Scale (MADRS):

The line graph (figure 03) shows that This decrease is statistically significant in both group but FDC of Acetyl-L-carnitine and Agmatine Sulfate provided more favorable outcomes compared to Escitalopram.

Clinicians Global Impressions (CGI) Score – Severity of Illness

There was a visible shift in the CGI severity of illness scores from moderately ill to mildly and borderline mentally ill conditions from Day 0 to Day 28, indicating better outcomes for the Acetyl-L-carnitine and Agmatine Sulfate group. (see Table 4)

Table 4: Change in number and proportion of subjects over severity of illness from Day 0 to 28

	Day 0	Day 28	Day 0	Day 28
	Acetyl-L-carnitine and Agmatine Sulfate		Escitalopram	
0 = Not assessed	0	0	0	0
1 = Normal, not at all ill	0	0	0	0
2 = Borderline mentally ill	0	16	0	10
3 = Mildly ill	1	13	0	18
4 = Moderately ill	28	0	29	2
5 = Markedly ill	1	0	1	0
6 = Severely ill	0	0	0	0
7 = Among the most extremely ill patients	0	0	0	0

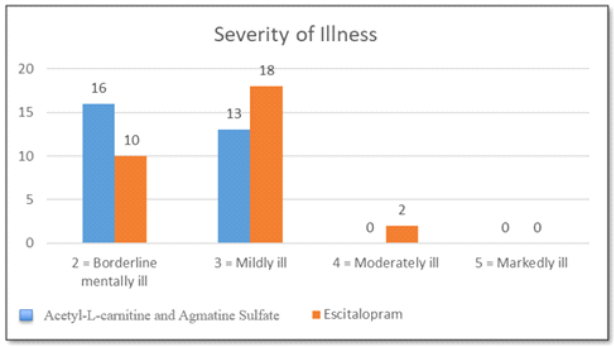

Figure 4: Sum of the Montgomery-Asberg Depression Rating Scale (MADRS):

In figure 04, there is a visible shift from moderately ill to mildly and borderline mentally ill condition from Day 0 to 28. This graph represents the number of patients at day 28 according to the severity of their illness, clearly demonstrating better outcomes for Acetyl-L-carnitine and AgmatineSulfategroup

Clinicians Global Impressions (CGI) Score – Global Improvement

By Day 28, 21 participants in the Acetyl-L-carnitine and AgmatineSulfategroup were rated as "much improved" compared to 11 participants in the Escitalopram group. Additionally, 8 participants in the Acetyl-L-carnitine and Agmatine Sulfategroup were "minimally improved," while 17 participants in the Escitalopram group fell into this category. Notably, 4 participants in the Escitalopram group showed no change, whereas all participants in the Acetyl-L-carnitine and Agmatine Sulfategroup exhibited some level of improvement, underscoring the superior outcomes of the Acetyl-L-carnitine and AgmatineSulfatetreatment. (see Table 5)

Table 5: Change in number and proportion of subjects over Global Improvement from day 0 to 28

	Day 0	Day 28	Day 0	Day 28
	Acetyl-L-carnitine and Agmatine Sulfate		Escitalopram	
0 = Not assessed	0	0	0	0
1 = Very much improved	0	0	0	0
2 = Much improved	0	21	0	11
3 = Minimally improved	0	8	0	17
4 = No change	30	0	30	2
5 = Minimally worse	0	0	0	0
6 = Much worse	0	0	0	0
7 = Very much worse	0	0	0	0

Safety and Adverse Events

The incidence of adverse events was lower in the Acetyl-L-carnitine and Agmatine Sulfategroup compared to the Escitalopram group. Only one participant in the Acetyl-L-carnitine and Agmatine Sulfategroup reported nausea and vomiting, while the Escitalopram group had a higher incidence of adverse events, including nausea and vomiting (3 participants), headache (1 participant), giddiness (1 participant), burning sensation (1 participant), and insomnia (1 participant). Overall, adverse events were reported in 7 participants in the Escitalopram group compared to 1 participant in the Acetyl-L-carnitine and Agmatine Sulfategroup.

Regarding the causality and severity of these adverse events in the Acetyl-L-carnitine and Agmatine Sulfategroup, the single adverse event was deemed unlikely related to the treatment and was mild in severity. In the Escitalopram group, 5 of the 7 adverse events were considered probable or likely related to the treatment, with all events being mild in severity. (see Table 6 and 7)

Table 6: Safety and Adverse events

	Acetyl-L-carnitine and Agmatine Sulfate (N=30)	Escitalopram (N=30)	Overall (N=60)
Nausea and vomiting	1 (100%)	3 (42.85%)	4 (50%)
Headache	0 (00.00%)	1 (14.28%)	1 (12.5%)
Giddiness	0 (00.00%)	1 (14.28%)	1 (12.5%)
Burning sensation	0 (00.00%)	1 (14.28%)	1 (12.5%)
Insomnia (Sleeplessness)	0 (00.00%)	1 (14.28%)	1 (12.5%)

Table 7: Causality and Severity of Adverse Events

	Acetyl-L-carnitine and AgmatineSulfate (N=30)	Escitalopram (N=30)	Overall (N=60)
All AEs	1 (100%)	7(100%)	8 (100%)
Causality			
4= Unlikely	1 (100%)	2 (28.57%)	3 (37.5%)
2= Probable/Likely	0 (00.00%)	5 (71.42%)	5 (62.5%)
Severity of AEs			
Grade 1= Mild	1 (100%)	7(100%)	8 (100%)

Lab Investigations

The laboratory investigations revealed no significant adverse effects related to the biochemical parameters monitored. In the Acetyl-L-carnitine and Agmatine Sulfategroup, the mean serum phosphate levels decreased slightly from 3.43 (SD 0.60) at baseline to 3.22 (SD 0.59) on Day 28. Similarly, the Escitalopram group showed a reduction in mean serum phosphate levels from 4.15 (SD 2.13) to 3.58 (SD 0.87). Serum calcium levels remained stable in both groups, with the Acetyl-L-carnitine and Agmatine Sulfategroup showing a minimal change from 9.66 (SD 0.50) to 9.62 (SD 0.41), and the Escitalopram group from 9.65 (SD 0.40) to 9.57 (SD 0.49).

Parathyroid hormone (PTH) levels decreased in both groups, from 64.79 (SD 38.77) to 59.79 (SD 30.30) in the Acetyl-L-carnitine and Agmatine Sulfategroup and from 61.01 (SD 26.23) to 54.24 (SD 21.81) in the Escitalopram group. HbA1c levels also showed a decrease, with the Acetyl-L-carnitine and AgmatineSulfategroup dropping from 6.17 (SD 1.56) to 5.87 (SD 1.22), and the Escitalopram group from 5.92 (SD 0.99) to 5.70 (SD 0.67).

For thyroid function, the Acetyl-L-carnitine and Agmatine Sulfategroup exhibited a slight increase in TSH levels from 2.95 (SD 4.52) to 3.39 (SD 7.62), while the Escitalopram group saw a decrease from 4.00 (SD 6.66) to 3.84 (SD 5.19). T3 levels remained stable in the Acetyl-L-carnitine and Agmatine Sulfategroup, changing minimally from 1.08 (SD 0.26) to 1.07 (SD 0.17), and slightly increased in the Escitalopram group from 1.01 (SD 0.24) to 1.03 (SD 0.16). T4 levels decreased in both groups, from 9.40 (SD 2.29) to 8.93 (SD 1.56) in the Acetyl-L-carnitine and Agmatine Sulfategroup and from 9.12 (SD 2.25) to 8.38 (SD 2.09) in the Escitalopram group.

Overall, these laboratory findings suggest that Acetyl-L-carnitine and Agmatine is not associated with significant adverse changes in key biochemical parameters, thereby supporting its favorable safety profile compared to Escitalopram.*(see Table 8)*

Table 8: Laboratory Investigation (Biochemical Estimations) at Day 0 and Day 28

	Day 0	Day 28	Change from day 0	Day 0	Day 28	Change from day 0
	Acetyl-L-carnitine and Agmatine Sulfate			Escitalopram		
Serum Phosphate Result						
Mean (SD)	3.43 (0.60)	3.22 (0.59)	-0.20 (-0.01)	4.15 (2.13)	3.58 (0.87)	-0.56 (-1.25)
p value	-	-	0.30	-	-	0.20
Serum Calcium Result						
Mean	9.66 (0.50)	9.62 (0.41)	-0.03 (-0.09)	9.65 (0.40)	9.57 (0.49)	-0.08 (0.08)
p value	-	-	0.91	-	-	0.46
PTH Result						
Mean (SD)	64.79 (38.77)	59.79 (30.30)	-5.00 (-8.47)	61.01 (26.23)	54.24 (21.81)	-6.76 (-4.42)
p value	-	-	0.42	-	-	0.07
HbA1c Result						
Mean (SD)	6.17 (1.56)	5.87 (1.22)	-0.29 (-0.33)	5.92 (0.99)	5.70 (0.67)	-0.22 (-0.32)
p value	-	-	0.21	-	-	0.03
TSH Result						
Mean	2.95 (4.52)	3.39 (7.62)	0.44 (3.09)	4.00 (6.66)	3.84 (5.19)	-0.16 (-1.46)
p value	-	-	0.51	-	-	0.63
T3 Result						
Mean	1.08 (0.26)	1.07 (0.17)	-0.01 (-0.08)	1.01 (0.24)	1.03 (0.16)	0.02 (-0.07)
p value	-	-	0.68	-	-	0.56
T4 Result						
Mean	9.40 (2.29)	8.93 (1.56)	-0.47 (-0.73)	9.12 (2.25)	8.38 (2.09)	-0.74 (-0.15)
p value	-	-	0.05	-	-	0.00

Discussion

The findings from this double-blind, randomized, controlled trial indicate that, a combination of Acetyl-L-carnitine and AgmatineSulfate, is a promising alternative to Escitalopram for the treatment of Major Depressive Disorder (MDD). The results demonstrated that FDC of Acetyl-L-carnitine and Agmatine Sulfate significantly improved depressive symptoms, as evidenced by the reductions in Hamilton Rating Scale for Depression (HAM-D17) and Montgomery-Asberg Depression Rating Scale (MADRS) scores over the 28-day treatment period.

The primary objective of the study was to determine whether Acetyl-L-carnitine and Agmatine Sulfate could provide greater reductions in depressive symptoms compared to Escitalopram.

The data showed that participants in the Acetyl-L-carnitine and Agmatine Sulfategroup experienced a more substantial decrease in HAM-D17 scores (mean change: -8.67± 1.35) compared to those in the Escitalopram group (mean change: -3.80± 1.98). Similarly, the MADRS scores exhibited a greater reduction in the Acetyl-L-carnitine and Agmatine Sulfategroup (mean change: -12.33) compared to the Escitalopram group (mean change: -9.66). These results underscore the superior efficacy of Acetyl-L-carnitine and Agmatine Sulfatein alleviating depressive symptoms.

Secondary objectives included assessing the safety and overall efficacy of FDC of Acetyl-L-carnitine and AgmatineSulfate. The Clinicians Global Impressions (CGI) scores supported the primary efficacy findings, showing a higher number of patients in the Acetyl-L-carnitine and Agmatine Sulfategroup who were rated as "much improved" by Day 28. Additionally, the incidence of adverse events was notably lower in the Acetyl-L-carnitine and AgmatineSulfategroup, with only one reported case of nausea and vomiting, compared to seven adverse events in the Escitalopram group. This highlights the favourable safety profile of Acetyl-L-carnitine and AgmatineSulfate. All reported adverse events were of mild in nature.

Vital signs, including pulse rate, body temperature, respiratory rate, and seated blood pressure, remained stable across both treatment groups, further supporting the tolerability of Acetyl-L-carnitine and AgmatineSulfate. The minor fluctuations observed in these parameters were not clinically significant, indicating that both treatments were well-tolerated without adverse impacts on these vital signs.

Though these findings are encouraging, the study has a number of limitations. The small sample size and short follow-up (28 days) limit generalizability and preclude and assessment of the long-term safety/efficacy of the FDC. Moreover, the lack of follow-up data after treatment completion limits our understanding of the long-lasting effects of Acetyl-L-carnitine and Agmatine Sulfate. In addition, the trial did not measure any economic impact of using this combination therapy versus Escitalopram, a key factor in real-life implications, especially in resource-limited environments.

The literature supports the potential of Acetyl-L-carnitine and Agmatine Sulfate as effective treatments for depression. Acetyl-L-carnitine has been shown to enhance neuroplasticity and improve depressive symptoms through epigenetic mechanisms, including the modulation of brain-derived neurotrophic factor (BDNF) levels and glutamatergic neurotransmission. [13,16-19]Studies indicate that low blood levels of Acetyl-L-carnitine are associated with the severity and duration of depression, suggesting its critical role in the pathophysiology of MDD [16]. Furthermore, research has demonstrated that Acetyl-L-carnitine produces rapid antidepressant effects, sometimes within days of administration, which is significantly faster than conventional antidepressants. [16]

Agmatine, on the other hand, modulates several neurotransmitter systems and exhibits rapid antidepressant effects. It has shown promise in preclinical models, influencing pathways involved in stress responses and inflammation, which are key factors in the development and maintenance of depressive symptoms. [14-15] Agmatine has also been found to have neuroprotective properties and can enhance the efficacy of other antidepressant treatments [20], making it a valuable component of combination therapies like Acetyl-L-carnitine and Agmatine Sulfate.The combination of these two compounds in REJIYANA® leverages their synergistic effects, offering a novel and effective treatment for MDD.

Based on these findings, larger, multi-center trials of long durations are warranted to ascertain the long-term safety and efficacy of this combination therapy. Dose optimization, drug interactions, and the economic aspects of the therapy should also be further studied in future clinical studies. For a better understanding of the extent of benefits, it would have been beneficial to do follow-up periods after treatment to comment on the long-term effects of Acetyl-L-carnitine and Agmatine Sulfate.

Conclusion

FDC of Acetyl-L-carnitine and Agmatine Sulfate showed better effectiveness and safety compared to Escitalopram for treating Major Depressive Disorder. It significantly reduced depressive symptoms and had fewer side effects, making it a promising

alternative to traditional SSRIs like Escitalopram. Further research is needed to confirm the long-term benefits and optimal dosage of Acetyl-L-carnitine and AgmatineSulfate combination. Given the current limitations of antidepressant treatments, Acetyl-L-carnitine and Agmatine Sulfate FDC offers a new and hopeful option for managing this challenging disorder.

Funding Sources: Celagenex Research (India) Pvt Ltd

Ethical Clearance: Ethics committee Name: Asha Hospital Ethics Committee

Registration No: ECR/lnst/AP/2013/RR-20 Valid Jan2025 EC Approval date of study: 16 Apr 2023

Conflicts of interest statement: NIL

References

1. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018 Nov 10;392(10159):1789-1858. doi: 10.1016/S0140-6736(18)32279-7. Epub 2018 Nov 8. Erratum in: Lancet. 2019 Jun 22;393(10190):e44. doi: 10.1016/S0140-6736(19)31047-5. PMID: 30496104; PMCID:
2. Nagy C, Maitra M, Tanti A, Suderman M, Théroux JF, Davoli MA, Perlman K, Yerko V, Wang YC, Tripathy SJ, Pavlidis P, Mechawar N, Ragoussis J, Turecki G. Single-nucleus transcriptomics of the prefrontal cortex in major depressive disorder implicates oligodendrocyte precursor cells and excitatory neurons. Nat Neurosci. 2020 Jun;23(6):771-781. doi: 10.1038/s41593-020-0621-y. Epub 2020 Apr 27. PMID: 32341540.
3. Fellinger M, Waldhör T, Serretti A, Hinterbuchinger B, Pruckner N, König D, Gmeiner A, Vyssoki S, Vyssoki B, Fugger G. Seasonality in Major Depressive Disorder: Effect of Sex and Age. J Affect Disord. 2022 Jan 1;296:111-116. doi: 10.1016/j.jad.2021.09.051. Epub 2021 Sep 22. PMID: 34600171.
4. Teufel F, Aggarwal A, Chwastiak L, Patel V, Ali MK. Depression Diagnosis, Treatment, and Remission Among Adults in India. JAMA Psychiatry. 2024 Dec 1;81(12):1265-1269. doi: 10.1001/jamapsychiatry.2024.3419. PMID: 39475926; PMCID: PMC11581718.
5. Yang, Jin-shuai& Zhang, Lu-yu& Yang, Cheng-hao & Li, Xin-yu& Li, Zhi-qiang. (2024). Global, Regional, and National Epidemiology of Depression in Working-Age Individuals, 1990–2019. Depression and Anxiety. 2024. 10.1155/2024/4747449.
6. Rice F, Riglin L, Lomax T, Souter E, Potter R, Smith DJ, Thapar AK, Thapar A. Adolescent and adult differences in major depression symptom profiles. J Affect Disord. 2019 Jan 15;243:175-181. doi: 10.1016/j.jad.2018.09.015. Epub 2018 Sep 11. PMID: 30243197.
7. Hasin DS, Sarvet AL, Meyers JL, Saha TD, Ruan WJ, Stohl M, Grant BF. Epidemiology of Adult DSM-5 Major Depressive Disorder and Its Specifiers in the United States. JAMA Psychiatry. 2018 Apr 1;75(4):336-346. doi: 10.1001/jamapsychiatry.2017.4602. PMID: 29450462; PMCID: PMC5875313.
8. Kautzky A, James GM, Philippe C, Baldinger-Melich P, Kraus C, Kranz GS, Vanicek T, Gryglewski G, Wadsak W, Mitterhauser M, Rujescu D, Kasper S, Lanzenberger R. The influence of the rs6295 gene polymorphism on serotonin-1A receptor distribution investigated with PET in patients with major depression applying machine learning. Transl Psychiatry. 2017 Jun 13;7(6):e1150. doi: 10.1038/tp.2017.108. PMID: 28608854; PMCID: PMC5537636.
9. McLachlan G. Treatment resistant depression: what are the options? BMJ. 2018 Dec 18;363:k5354. doi: 10.1136/bmj.k5354. PMID: 30563939.
10. Chu A, Wadhwa R. Selective Serotonin Reuptake Inhibitors. 2023 May 1. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan–. PMID: 32119293.
11. Liu T, Deng K, Xue Y, Yang R, Yang R, Gong Z, Tang M. Carnitine and Depression. Front Nutr. 2022 Mar 14;9:853058. doi: 10.3389/fnut.2022.853058. PMID: 35369081; PMCID: PMC8964433.
12. Nasca C, Bigio B, Lee FS, Young SP, Kautz MM, Albright A, Beasley J, Millington DS, Mathé AA, Kocsis JH, Murrough JW, McEwen BS, Rasgon N. Acetyl-l-carnitine deficiency in patients with major depressive disorder. Proc Natl Acad Sci U S A. 2018 Aug 21;115(34):8627-8632. doi: 10.1073/pnas.1801609115. Epub 2018 Jul 30. PMID: 30061399; PMCID: PMC6112703.

13. Valverde AP, Camargo A, Rodrigues ALS. Agmatine as a novel candidate for rapid-onset antidepressant response. World J Psychiatry. 2021 Nov 19;11(11):981-996. doi: 10.5498/wjp.v11.i11.981. PMID: 34888168; PMCID: PMC8613765.

14. Watts D, Pfaffenseller B, Wollenhaupt-Aguiar B, Paul Géa L, Cardoso TA, Kapczinski F. Agmatine as a potential therapeutic intervention in bipolar depression: the preclinical landscape. Expert Opin Ther Targets. 2019 Apr;23(4):327-339. doi: 10.1080/14728222.2019.1581764. Epub 2019 Feb 22. PMID: 30764678.

15. Bigio B, Azam S, Mathé AA, Nasca C. The neuropsychopharmacology of acetyl-L-carnitine (LAC): basic, translational and therapeutic implications. Discov Ment Health. 2024 Jan 2;4(1):2. doi: 10.1007/s44192-023-00056-z. PMID: 38169018; PMCID: PMC10761640.

16. Nie L-J, Liang J, Shan F, Wang B-S, Mu Y-Y, Zhou X-H and Xia Q-R (2021) L-Carnitine and Acetyl-L-Carnitine: Potential Novel Biomarkers for Major Depressive Disorder. Front. Psychiatry 12:671151. doi: 10.3389/fpsyt.2021.671151

17. Saelens J, Gramser A, Watzal V, et al. Relative effectiveness of antidepressant treatments in treatment-resistant depression: a systematic review and network meta-analysis of randomized controlled trials. Neuropsychopharmacology :Official Publication of the American College of Neuropsychopharmacology. 2024 Dec. DOI: 10.1038/s41386-024-02044-5. PMID: 39739012.

18. Bigio B, Azam S, Mathé AA, Nasca C. The neuropsychopharmacology of acetyl-L-carnitine (LAC): basic, translational and therapeutic implications. Discov Ment Health. 2024 Jan 2;4(1):2. doi: 10.1007/s44192-023-00056-z. PMID: 38169018; PMCID: PMC10761640.

19. Harish, K. H., & Swamy, A. H. V. (2024). Agmatine as a Promising Neuroprotective Strategy for Treating Neurological Disorders. International Journal of Pharmaceutical Investigation, 14(3), 670–680. https://doi.org/10.5530/ijpi.s14.3.78.