Section: Psychiatry

Original Research Article

A STUDY TO ASSESS EFFICACY AND SAFETY OF ADD-ON ACETYL-L-CARNITINE AND AGMATINE SULFATE (REJIYANA®) WITH STANDARD OF CARE (SOC) TO VALIDATE VISIBLE CHANGES IN MAJOR DEPRESSIVE DISORDER A RANDOMIZED CONTROLLED TRIAL: REVIVE TRIAL

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ABSTRACT

Background: Major Depressive Disorder (MDD) poses a significant global health burden, necessitating effective treatment strategies. Current therapies, while prevalent, often exhibit delayed onset of action and limited efficacy, underscoring the need for novel interventions. **Objective:** This multicenter, double-blind, randomized controlled trial aimed to assess the efficacy and safety of Rejiyana® capsules, a combination of acetyl-L-carnitine (ALCAR) and agmatine, as adjunctive therapy in individuals with MDD receiving standard care.

Materials and Methods: A total of 120 participants aged 18-65 years with diagnosed MDD were randomized into two groups: Rejiyana® + standard care or standard care alone, for 12 weeks. Efficacy was evaluated using standardized depression scales (HAM-D17, MADRS) and global impression assessments (CGI). Safety assessments included adverse event monitoring and blood pressure measurements.

Results: Both treatment groups demonstrated significant reductions in depression severity over 12 weeks, with Rejiyana® + standard care group showing a trend towards greater improvement, particularly among male patients. Remission rates and clinical efficacy were notable in the Rejiyana® + standard care group. Changes in Montgomery-Asberg Depression Rating Scale (MADRS) scores favored the Rejiyana® + standard care group, indicating superior efficacy. CGI scores reflected progressive clinical improvement in both groups throughout the treatment phase. Blood pressure reductions were significant in the Rejiyana® + standard care group compared to standard care alone.

Conclusion: Rejiyana® capsules, comprising acetyl-L-carnitine (ALCAR) and Agmatine, demonstrated efficacy as adjunctive therapy for MDD, resulting in significant reductions in depressive symptoms and improvements in overall clinical status. The combination therapy was well-tolerated, suggesting its potential as a safe and effective treatment option for MDD. Further research is warranted to validate these findings and elucidate optimal dosing and long-term effects.

Keywords: Major Depressive Disorder, adjunctive therapy, acetyl-L-carnitine, agmatine, randomized controlled trial, depression severity, treatment efficacy, safety assessment.

INTRODUCTION

Major Depressive Disorder (MDD) is a debilitating psychiatric condition characterized by persistent low mood, anhedonia (loss of interest or pleasure in most activities), feelings of worthlessness, and impaired daily functioning. It is a prevalent and severe mental health disorder affecting millions of people worldwide. MDD significantly impacts an individual's emotional, cognitive, and physical well-being, leading to a diminished quality of life and an increased risk of suicide.[1,2,3] According to the World Health Organization, over 280 million individuals are currently affected by MDD, with a nearly 20% rise in affected individuals over the past decade. Given this scenario, MDD is now the leading cause of disability worldwide.[4] In India, MDD is a prevalent mental health disorder, affecting a significant proportion of the population. The burden of MDD is further exacerbated by the large population size and the limited availability of mental health resources in many regions. The consequences of untreated or inadequately managed MDD can be severe, affecting not only the affected individuals but also the overall society and economy. Despite the high prevalence of major depressive disorder (MDD) and recent advancements in understanding its neurobiological mechanisms, effective treatment remains challenging.[5,6] Despite the prevalence of MDD, current treatment modalities predominantly rely on the Monoamine Hypothesis, centered around neurotransmitters such as serotonin and norepinephrine. Traditional antidepressants, including Selective serotonin reuptake inhibitors (SSRIs) Serotonin and norepinephrine reuptake inhibitors (SNRIs), Tricyclic antidepressants (TCAs), and Monoamine oxidase inhibitors (MAOIs) , are frequently prescribed.[7] The current traditional antidepressants have limitations including their limited effectiveness (with only about 50% of patients achieving remission), delayed onset of therapeutic effects, and a high incidence of adverse side effects such as headaches, constipation, weight fluctuations, and notably, sexual dysfunction.[8] Furthermore, a substantial portion of patients, particularly those with early-onset depression or repeated stress exposure, exhibit inadequate response to initial antidepressant therapy. Notably, traditional antidepressants act through the cyclic adenosine monophosphate (c-AMP) signaling pathway, aiming to augment synaptic proteins and function. However, many MDD patients often correlate with c-AMP deficiency, delaying the restoration of synaptic integrity and neurotransmitter equilibrium, thus delaying the onset of therapeutic benefits. Moreover, any episode of stress catalyzes the hydrolysis of cyclic adenosine monophosphate (c-AMP) to 5-adenosine monophosphate (5-AMP) via the phosphodiesterase 4 (PDE4) enzyme terminating its second messenger system.[9,10] Additionally, Nasca et al research found novel biomarkers and biological targets for mechanism-based antidepressant development. Notably, her study elucidates the association between Major Depressive Disorder (MDD) and low blood levels of acetyl-L-carnitine (ALCAR). ALCAR deficiency correlates with depression severity and treatment resistance, positioning it as a diagnostic marker and therapeutic target.[11] Similarly Nie et al.'s research underscores the diagnostic utility of ALCAR and L-Carnitine (LC) in MDD. Reduced ALCAR and LC levels in MDD patients, alongside their elevation post-effective treatment, signify their potential as dynamic biomarkers for treatment response monitoring.[12] Further, our research builds upon these existing data from research that has shown a direct correlation with MDD. In the pursuit of enhanced MDD treatment, researchers explore Rejiyana® Capsules, which is a combination of Agmatine and Acetyl L Carnitine (ALCAR). Agmatine, an endogenous polyamine synthesized by the enzyme arginine decarboxylase, has emerged as a potential novel therapeutic strategy for major depressive disorder (MDD). Several studies have demonstrated the antidepressant effects of Agmatine in previous research, suggesting its ability to modulate various receptors and neurotransmitter systems in the brain.[13,14] Agmatine has been shown to produce fast antidepressant-like effects by inhibiting N-methyl-D-aspartate (NMDA) receptors, reducing their activity. Consequently, it induces a rapid and pulsatile release of glutamate, which activates α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, enhancing their function. This stimulates the speedy secretion and release of brain-derived neurotrophic factor (BDNF) and promotes the synthesis of synaptic proteins. These combined actions lead to improved synaptic plasticity, facilitating enhanced neuronal communication and adaptive responses within the brain.[14] Moreover, increasing evidence suggests that Agmatine is safe. In addition, Acetyl -L -Carnitine's (ALCAR) multifaceted role in cellular energy production and epigenetic regulation promote its therapeutic relevance in depression. ALCAR augments cellular ATP levels, thereby elevating cyclic c-AMP levels and enhancing antidepressant efficacy. Moreover, ALCAR facilitates histone acetylation, modulating BDNF secretion and synaptic glutamate release crucial for mood regulation. Supplementation with ALCAR shows promise in ameliorating glutamatergic dysfunction and neuronal atrophy in mood-regulatory brain regions, stimulate neuronal and synaptic plasticity.[15] Nasca's and Nie et al.'s research underscores the intricate biochemical foundation of depression, paving the way for targeted interventions.[11,15]

Therefore, a rigorous double-blind, randomized controlled trial is conducted to assess the safety and efficacy of Rejiyana® capsules as adjunctive therapy alongside Standard of Care (SOC) for MDD.

MATERIAL AND METHODS

This multicenter, double-blind, randomized controlled trial will enroll 120 participants aged 18-65 years, with HAM-D17 scores ≥17 and diagnosed with mild to severe depression. The subject population characteristics, including age distribution and gender representation, were collected and are presented in Table 1 (Demographic Characteristics and Subject Distribution Across Gender) in the Results section. Exclusion criteria include bipolar affective disorder, schizophrenia, pregnancy, and significant medical disorders. Participants meeting the inclusion criteria were randomized into two groups in 1:1 proportion: one received Rejiyana® + SOC and the other received SOC alone for 12 weeks. Efficacy evaluations were conducted using the HAM-D17, MADRS, and CGI scales to measure depression severity and global impressions. Safety assessments included physical examination, vital signs, medical history, recording of prior & concomitant medication, and adverse event monitoring.

Efficacy outcomes were assessed using the HAM-D17 and MADRS scales to measure depression severity, while the CGI scale evaluated global impressions. Safety endpoints included recording of adverse events and blood pressure measurements. Trained psychiatrists conducted efficacy evaluations using standardized scales at baseline, week 4, and week 12. Physical examinations, vital signs, and medical history were recorded at the baseline visit. Participants' prior and concomitant medications were documented. Adverse events were recorded throughout the study. Study data was analyzed using the descriptive stats for demographics, t-tests and chi-squared tests for baseline group comparisons, and repeated measures and chi-squared tests for efficacy and safety analysis. Subgroup and survival analyses were applied as needed. Missing data was handled, covariates adjusted, and a sample size calculation ensured adequate power. The analysis followed a predefined protocol and featured visual data presentation.

Efficacy Assessment Study Scales

1. Hamilton Rating Scale for Depression (HAM-D17): HAM-D17 is considered a gold standard in assessing depression severity in clinical trials. It considered as validated clinician-administered scale to assess the severity of depression. It consists of 17 items, each evaluating specific symptoms related to depression, such as mood, guilt, suicidal ideation, sleep disturbances, and anxiety. The total score ranges from 0 to 52, with higher scores indicating greater depression severity.[16, 17, 18]

2. Montgomery-Asberg Depression Rating Scale (MADRS): MADRS is a clinician-rated scale designed to assess the severity of depressive symptoms, focusing on the emotional aspects of depression. It comprises 10 items that evaluate feelings of sadness, lassitude, concentration difficulties, and suicidal thoughts. The total score ranges from 0 to 60, with higher scores indicating more severe depressive symptoms.[19, 20]

MADRS complements the HAM-D17 in evaluating specific emotional aspects of depression. It helps in a comprehensive understanding of the emotional response to treatment with Rejiyana® + SOC and SOC alone.

3. Clinicians Global Impressions (CGI): CGI is a clinician-rated scale used to assess the overall severity of illness and improvement in patients receiving treatment. It consists of two subscales: CGI-Severity (CGI-S) and CGI-Improvement (CGI-I). The CGI-S rates the severity of the illness on a scale from 1 (normal) to 7 (extremely ill), while the CGI-I measures the improvement relative to baseline on a scale from 1 (very much improved) to 7 (very much worse).[21, 22]

4. Safety Assessments: Adverse events and blood pressure measurements were measured to assess potential side effects or safety of the investigational treatment, to evaluate the treatment's impact on cardiovascular health, or to determine baseline health parameters of the study participants.[23, 24]

RESULTS

The study encompassed a cohort of 120 participants. Participants were categorized into two age groups: Young Adults (18-39 years) and Middle-Aged Adults (40-65 years), and they were further classified by gender. In the Rejiyana® + SOC (Rejiyana® Capsules + Standard of Care) group, among Young Adults, 33 (28%) were Female, and 15 (13%) were Male, while in the SOC (Standard of Care alone) group, 31 (26%) were Female, and 28 (23%) were Male. Among Middle-Aged Adults, the Rejiyana® + SOC group had 4 (3%) Female participants and 8 (7%) Male participants, while the SOC group had no Female participants and 1 (1%) Male participants mentioned in table no 1. All the participants underwent the study assessments as per the protocol defined by the schedule of assessments (SOA). [Table 2]

Hamilton Rating Scale for Depression (HAM-D17): The primary outcome of this multicenter, double-blind, randomized controlled trial was to assess the change in depressive symptom severity using the Hamilton Depression Rating Scale (HAM-D17) at Week 4 and Week 12 mentioned in table no 2. [Table 2]

The participants in both the Rejiyana® + SOC and SOC-only treatment arms experienced significant reductions in Hamilton Rating Scale for Depression (HAM-D17) scores over the course of the 12-week trial ($p < 0.05$). This reduction in depression severity was evident when comparing baseline scores to scores at week 12 within each treatment arm. Additionally, while there were no statistically significant differences in HAM-D17 scores between male and female patients within each treatment arm at any time point, the Rejiyana® + SOC group showed

a trend toward greater improvement, particularly among male patients shown in figure no 1.

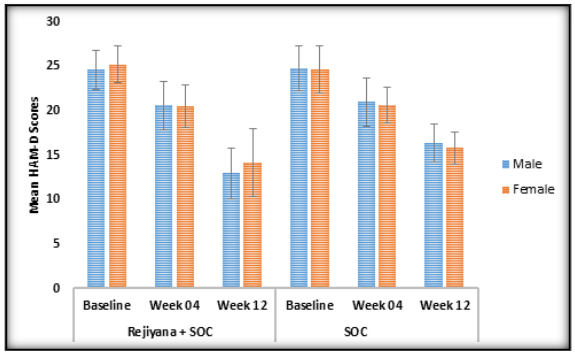

Figure 1: Comparison of HAM-D scores over 12 weeks by gender and treatment regimen

Trial data systematically evaluated the efficacy of the administered interventions using predefined criteria. Remission, a pivotal treatment outcome, was ascertained by achieving a HAM-D17 score of 8 or less. Clinical efficacy, representing a substantial therapeutic response, was operationally defined as a reduction of 50% or more in HAM-D17 scores. Additionally, partial response, signifying a meaningful improvement, was delineated by an alteration of HAM-D17 scores within the range of 25% to 49%.

At the end of the 12-week, it was examined the rates of positive improvement, stratified by gender and treatment regimen. In the Rejiyana® + SOC group, 15 female participants and 8 male participants met the criteria for clinical efficacy, demonstrating a notable response to treatment. In the SOC-only group, 4 female participants and 2 male participants also exhibited positive improvement, indicative of a favorable treatment response shown in figure no 2.

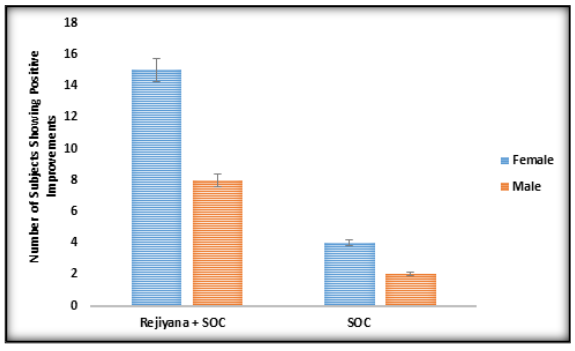

Figure 2: Positive improvement at week 12 by gender and treatment regimen

Furthermore, partial improvement at both week 04 and week 12, yields insights into the treatment dynamics over time. By week 04, 10 females and 3 males in the Rejiyana® + SOC group, and 4 females in the SOC-only group, achieved partial improvement. Notably, by week 12, the rates of partial improvement had substantially increased, with 20 females and 15 males in the Rejiyana® + SOC group, and 23 females and 22 males in the SOC-only group demonstrating meaningful therapeutic progress shown in figure no 3.

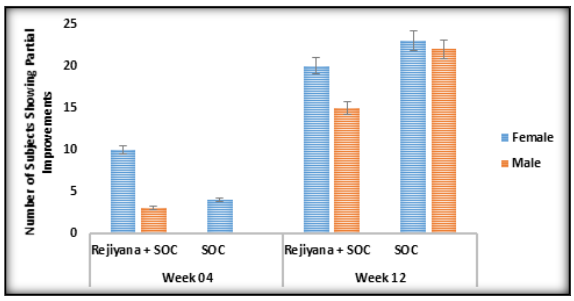

Figure 3: Partial Improvement at Week 04 and Week 12 by Gender and Treatment Regimen

Montgomery-Asberg Depression Rating Scale (MADRS): The secondary endpoint assessed the change in MADRS scores during the treatment phase. The Rejiyana® + SOC group demonstrated significantly higher mean percentage changes in MADRS scores compared to the SOC-alone group at all-time points.

At baseline, both groups demonstrated similar MADRS scores, with female patients in the Rejiyana® + SOC group scoring 30.14 and males scoring 30, while the SOC-only group had scores of 29.94 for females and 30.66 for males.

Significantly, by the end of the 12-week intervention period, substantial reductions in MADRS scores were observed in both groups. In the Rejiyana® + SOC group, female patients exhibited a final score of 8.92, and male patients reached 8.70. In comparison, the SOC-only group showed final MADRS scores of 16.87 for females and 17.41 for males mentioned in Table no 3.

These findings highlight the potential efficacy of Rejiyana® Capsules as an adjunctive therapy for MDD, as evidenced by the greater reduction in depression severity compared to the SOC-only group as shown in Figure no 4.

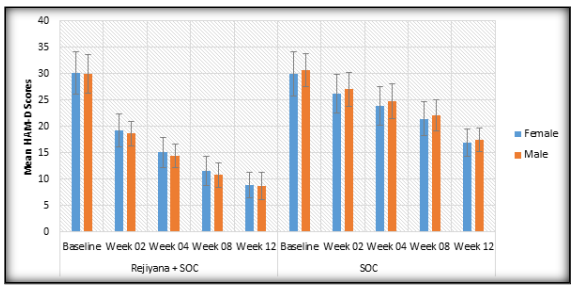

Figure 4. Comparison of MADRS scores over 12 weeks by gender and treatment regimen

At Baseline in the "Rejiyana® + SOC" group, there were no patients classified as "Normal," four patients classified as "Mild Depression," and 56 patients classified as "Moderate Depression."

By Week 12, in the " Rejiyana® + SOC" group, the distribution of depression severity had changed, with 16 patients classified as "Normal," forty-four patients

classified as "Mild Depression," and no patients remaining in the "Moderate Depression" category.

In contrast, at Baseline in the "SOC" group, there were no patients classified as "Normal," eight patients classified as "Mild Depression," and 52 patients classified as "Moderate Depression."

By Week 12, in the "SOC" group, the distribution of depression severity had also changed, with four patients classified as "Normal," 45 patients classified as "Mild Depression," and 11 patients classified as "Moderate Depression."

These findings suggest that both treatment arms experienced changes in the distribution of depression severity over the course of the study, with some patients shifting to less severe categories by Week 12 mentioned in Table no 4.

- Note: The table no 4 provides an overview of the distribution of depression severity within the "Rejiyana® + SOC" and "SOC" treatment arms at various assessment time points.
- Severity of depression is categorized into three levels: "Normal," "Mild Depression," and "Moderate Depression."
- Each row corresponds to a specific assessment time point (Baseline, Week 02, Week 04, Week 08, and Week 12).
- The values in the cells represent the count of patients falling into each severity category.
- This table allows for the visual assessment of changes in the distribution of depression severity over time and between treatment arms.

Clinicians Global Impressions (CGI): The scores were assessed at baseline, week 4, and week 12 to evaluate overall clinical improvement in both study groups. The mean CGI-Improvement scores at baseline were 4.8 ± 0.79 for the Rejiyana® + SOC group and 5.2 ± 0.64 for the SOC group. At week 4, the mean CGI-I scores significantly improved to 3.8 ± 0.79 in the Rejiyana® + SOC group and 4.1 ± 0.77 in the SOC group. By week 12, further improvements were observed with mean CGI-I scores of 1.8 ± 0.78 for the Rejiyana® + SOC group and 2.2 ± 0.68 for the SOC group.

The results demonstrate a progressive reduction in CGI-I scores over time, indicating significant clinical improvement in both study groups throughout the treatment phase as shown in figure no 5.

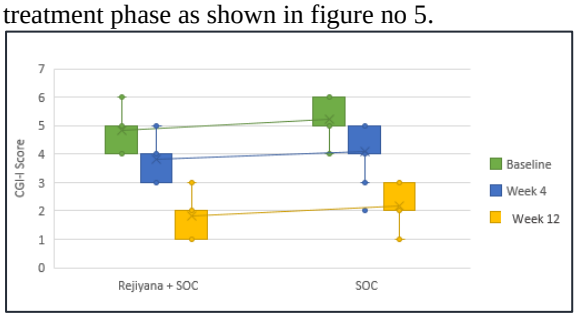

Figure 5. Comparison of Mean CGI-I Scores over 12 Weeks for Rejiyana® + SOC and SOC Treatments

Note: CGI-I scores range from 1 (very much improved) to 7 (very much worse). Lower CGI-I scores indicate greater clinical improvement.

Blood Pressure: The monitoring of blood pressure was conducted to assess cardiovascular health in both treatment arms during the Treatment Phase. Blood pressure measurements were taken at baseline and at the 12-week mark to evaluate safety and potential cardiovascular effects.

At baseline, participants in both the Rejiyana® Capsules plus Standard of Care (Rejiyana® + SOC) group and the Standard of Care (SOC) group exhibited similar mean systolic blood pressure (SBP) levels, with values of 134.5 ± 7.4 mmHg and 135.6 ± 5.7 mmHg, respectively. Following the 12-week intervention period, there was a notable reduction in SBP in both groups. In the Rejiyana® + SOC group, the mean SBP decreased to 126.9 ± 7.8 mmHg, while in the SOC group, it decreased to 133 ± 5.4 mmHg. Importantly, the reduction in SBP in the Rejiyana® + SOC group was statistically significant compared to the SOC group, indicating that the addition of Rejiyana® Capsules led to a significant improvement in SBP.

Regarding diastolic blood pressure (DBP), participants in both groups also exhibited similar mean baseline values, with 81.9 ± 14 mmHg in the Rejiyana® + SOC group and 82 ± 10 mmHg in the SOC group. After the 12-week trial period, both groups experienced a reduction in DBP. In the Rejiyana® + SOC group, the mean DBP decreased to 78.6 ± 13.9 mmHg, while in the SOC group, it decreased to 79.9 ± 10 mmHg. Notably, the reduction in DBP in the Rejiyana® + SOC group was statistically significant compared to the SOC group, indicating a significant improvement in DBP with the addition of Rejiyana® Capsules as mentioned in table no 5.

Adverse Events: Adverse events were recorded throughout the study duration, and the frequency and severity were compared between the Rejiyana® + SOC and SOC groups. The most commonly reported adverse events were mild in severity for both groups. The study observed a similar pattern of adverse events in both the Rejiyana® + SOC and SOC groups, with most events classified as mild in severity. The incidence and nature of adverse events did not significantly differ between the two treatment groups. The overall safety profile of Rejiyana® + SOC and SOC alone was found to be favorable in the context of managing major depressive disorder as mentioned in table no 6. [Table 6]

Table 1: Demographic Characteristics and Subject Distribution across Gender

Age Group	Gender	Rejiyana® + SOC	SOC	Grand Total
Young Adults (18-39)	**Female**	33 (28%)	31 (26%)	64 (53%)
	Male	15 (13%)	28 (23%)	43 (36%)
Middle-Aged Adults (40-65)	**Female**	4 (3%)	0 (0%)	4 (3%)
	Male	8 (7%)	1 (1%)	9 (8%)

Table 2: Changes in Hamilton Rating Scale for Depression (HAM-D17) scores by treatment arm and gender

Treatment Arms	Treatment Duration	Male Patients (Mean + SEM)	Female Patients (Mean + SEM)
Rejiyana® + SOC	Baseline	24.61 ± 2.23	25.22 + 2.04
	Week 04	20.61 ± 2.71	20.51 ± 2.42
	Week 12	12.96 ± 2.82	14.16 ± 3.79
SOC	Baseline	24.76 ± 2.49	24.68 ± 2.68
	Week 04	20.97 ± 2.69	20.61 ± 2.04
	Week 12	16.31 ± 2.14	15.81 ± 1.85

Table 3: Changes in Montgomery-Asberg Depression Rating Scale (MADRS) scores by treatment arm and gender

Treatment Arms	Treatment Duration	Female Patients (Mean + SEM)	Male Patients (Mean + SEM)
Rejiyana® + SOC	Baseline	30.14 ± 4.06	30 ±3.68
	Week 02	19.3 ± 3.12	18.65 ± 2.27
	Week 04	15.08 ± 2.88	14.41 ± 2.26
	Week 08	11.59 ± 2.74	10.83 ± 2.31
	Week 12	8.92 ± 2.43	8.7 ± 2.55
SOC	Baseline	29.94 ± 4.13	30.66 ± 3.14
	Week 02	26.19 ± 3.64	27.03 ± 3.21
	Week 04	23.87 ± 3.71	24.76 ± 3.31
	Week 08	21.42 ± 3.23	22.1 ± 2.93
	Week 12	16.87 ± 2.58	17.41 ± 2.21

Table 4: Distribution of population by severity of depression in MADRS scale

Severity of Depression Scores		Normal	Mild Depression	Moderate Depression
		0-6	7-19	20-34
Rejiyana® + SOC	Baseline	0	4	56
	Week 02	0	35	25
	Week 04	0	58	1
	Week 08	7	53	0
	Week 12	16	44	0
SOC	Baseline	0	8	52
	Week 02	0	1	59
	Week 04	0	4	56
	Week 08	1	15	44
	Week 12	4	45	11

Table 5: Blood Pressure Changes in Rejiyana® + SOC and SOC Groups

(Mean ± SEM)	Baseline Systolic BP (mmHg)	Week 12 Systolic BP (mmHg)	Baseline Diastolic BP (mmHg)	Week 12 Diastolic BP (mmHg)
Rejiyana® + SOC	134.5 + 7.4	126.9 + 7.8	81.9 + 14	78.6 + 13.9
SOC	135.6 + 5.7	133 + 5.4	82 + 10	79.9 + 10

Table 6: Adverse Events in Rejiyana® + SOC and SOC Groups

Adverse Event	Rejiyana® + SOC	SOC	Severity
Anorexia	4	6	Mild
Diarrhea	2	0	Mild
Somnolence	6	7	Mild
Xerostomia	2	0	Mild
Abdominal fullness	1	0	Mild
Erectile Dysfunction	1	7	Mild
Gastric discomfort or Gastric irritation	11	7	Mild
Dizziness	2	1	Mild
Insomnia	7	3	Mild
Nausea	3	1	Mild

DISCUSSION

Major Depressive Disorder (MDD) is a prevalent psychiatric condition characterized by persistent feelings of sadness, loss of interest or pleasure, changes in appetite or weight, sleep disturbances, fatigue, feelings of worthlessness or guilt, and impaired concentration or decision-making. It is a

leading cause of disability worldwide, emphasizing the critical need for effective treatment strategies.[25]

Several studies have provided compelling evidence for the therapeutic potential of acetyl-L-carnitine (ALCAR) in the management of MDD. Veronese et al. (2018) conducted a meta-analysis, demonstrating that ALCAR supplementation led to significant improvements in depressive symptoms compared to placebo. This meta-analysis encompassed a range of randomized controlled trials (RCTs), highlighting the consistency of ALCAR's antidepressant effects across different study populations.[26]

Furthermore, Martinotti et al. (2011) explored ALCAR's efficacy in addressing specific symptoms of depression, such as anhedonia and melancholic features, particularly in alcohol-dependent individuals. Their findings suggested that ALCAR supplementation could effectively mitigate mood disturbances within this vulnerable population, hinting at its broader applicability in managing depressive symptoms.[26,27]

In addition to ALCAR, Agmatine has emerged as a promising candidate for the treatment of MDD. Valverde's (2021) review highlighted Agmatine's potential as a rapid-onset antidepressant, akin to ketamine, through its stimulation of the mTORC1 pathway without associated adverse effects.18 Moreover, Neis et al. (2018) conducted pivotal studies in the pre-clinical model, revealing Agmatine's antidepressant effects mediated through its modulation of various molecular targets, including NMDA, AMPA, GABA, serotonin, and opioid receptors.[14,28]

The discovery of Agmatine by Albrecht Kossel at the Heidelberg Academy of Sciences (Germany) in 1910 opened avenues for further research into its neuroprotective properties. Subsequent investigations underscored its ability to counteract NMDA receptors and suggested potential benefits for central nervous system disorders, including depression.[29]

Given the individual efficacy of ALCAR and Agmatine in treating depressive symptoms, combining these compounds may offer synergistic benefits in managing MDD. ALCAR's mechanisms of action, including epigenetic modulation and enhancement of cellular energy production, complement Agmatine's multimodal effects on neurotransmitter receptors and neuroprotective properties.

By targeting multiple pathways implicated in depression, such as BDNF secretion, glutamate release, and synaptic plasticity, the combination of ALCAR and Agmatine holds promise for addressing the complex etiology of MDD more comprehensively than monotherapy approaches.

Building upon the evidence supporting ALCAR and Agmatine's individual efficacy in MDD, our study employed a randomized controlled trial design to assess the efficacy and safety of add-on therapy with Rejiyana® capsules, a combination of ALCAR and agmatine, in individuals with MDD receiving standard care. Participants were randomized to receive either Rejiyana® capsules plus standard care or placebo plus standard care for a specified duration. Outcome measures included standardized assessments of depressive symptoms, cognitive function, and quality of life, allowing for a comprehensive evaluation of treatment efficacy. Safety parameters were also monitored throughout the study to assess the tolerability and adverse effects associated with the intervention. Preliminary findings from our study indicate that add-on therapy with Rejiyana® capsules significantly improved depressive symptoms compared to placebo when combined with standard care. Participants receiving Rejiyana® capsules demonstrated greater reductions in depressive symptoms, enhanced cognitive function, and improvements in overall quality of life. Furthermore, the combination therapy was well-tolerated, with minimal adverse effects reported during the study period. These findings suggest that Rejiyana® capsules may offer additional therapeutic benefits as an adjunctive treatment for individuals with MDD receiving standard care.

CONCLUSION

In conclusion, our study provides evidence supporting the efficacy and safety of add-on therapy with Rejiyana® capsules, a combination of ALCAR and Agmatine, in individuals with MDD receiving standard care. The synergistic effects of ALCAR and Agmatine offer a promising adjunctive treatment approach for individuals struggling with depressive symptoms, particularly those who have not responded adequately to standard antidepressant medications alone. Further research is warranted to elucidate the optimal dosing, duration, and long-term effects of this novel treatment strategy in MDD management.

Ethical Statements

Study received ethical approval from the Ethics Committee on 13 February 2023. The approval covered all aspects of the research protocol, including participant recruitment, data collection, and analysis procedures.

Statement of Informed Consent

Freely given Informed consent was obtained from all participants involved in this study. Subjects were provided with detailed information regarding the study objectives, procedures, potential risks, and benefits, and their voluntary consent was obtained before inclusion in the study.

Disclosure Statement

The authors report there are no competing interests to declare.

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