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The Journal of *Medical Advancements and Research*

Articles:

Editorial

Not just the baby blues – increasing attention to perinatal mental health

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CONFLICTS OF INTEREST STATEMENT

None of the above authors have any conflicts of interest to report regarding this case report.

ABSTRACT

Discussion on the shift in focus on peripartum mental health.

Keywords: peripartum, postpartum depression, postpartum psychosis

The June 2025 issue of the American Journal of Psychiatry included articles and editorials with an emphasis on the most common perinatal mental health condition (postpartum depression (PPD)) and the most dangerous (postpartum psychosis (PPP)). Mental health conditions are the most common pregnancy complication in the United States, impacting at least 15% of all pregnancies (PSI 2025, Shorey et al. 2018). They are the leading underlying cause of death in the first year postpartum both in the United States (CDC 2024) and in the state of Kansas (KMMRC 2025). When mental health conditions go untreated in the perinatal period, we see lasting impact on the physical, cognitive, and emotional health and development of children (Figueiredo & Costa 2009, Figueiredo et al. 2017, Henrichs et al. 2011, Cao et al. 2014, Moss et al. 2017).

In Kansas, 14% of women surveyed by the Pregnancy Risk Assessment Monitoring System (PRAMS) within the 6 months after giving birth felt that they needed mental health treatment but did not receive it during their recent pregnancies (KDHE 2023). Perinatal mood and anxiety disorders are also implicated in substance use during pregnancy. For example, amongst women who smoked in the perinatal period, 38.5% cited worsening depression as the primary barrier to quitting, while 54% cited worsening anxiety as their primary barrier. This puts us, as psychiatrists, in a unique position where we can make a tremendous impact on the health and well-being of families across our state and the nation.

The article Stratifying Risk for Postpartum Depression at Time of Hospital Discharge (Clapp et al., 2025) describes a machine learning-based PPD risk model to predict which patients would develop PPD. The model utilized sociodemographic factors

(besides race and ethnicity, medical history, medication history prior to delivery, and Edinburgh Postnatal Depression Scale (EPDS) scores obtained during pregnancy to determine risk. The American College of Obstetricians and Gynecologists (ACOG) recommends that women be screened for PPD multiple times throughout the course of pregnancy as well as after delivery (ACOG 2023). In real-world practice, very few patients are screened with this frequency. This machine-learning model represents promising initial efforts to close the gap in identifying women who may be at risk for PPD. These efforts should reinforce, rather than replace, screening by physicians in clinical settings.

In their article Familial Risk for Postpartum Psychosis, Kępińska et al. (2025) similarly describe efforts to predict who may be at risk for developing Postpartum Psychosis (PPP). Postpartum psychosis is blessedly rare but is one of the most serious psychiatric emergencies that exists, with significantly elevated risk for suicide and infanticide (Bergink et al. 2016). Postpartum psychosis has been linked to personal and family history of bipolar disorder, but in many cases, patients, families, and medical professionals are caught off-guard when symptoms develop. In this case, researchers also identified increased relative risk for developing PPP in women with a sister who experienced the condition. It represents an important, albeit small, step in elucidating and eventually preventing this deadly disorder.

While it is heartening to see such attention drawn to these vital areas of women's health, these articles also highlight how much is unknown, and how much has been overlooked, in the realm of perinatal mental health. Given the associated morbidity and mortality, I am hopeful that psychiatry as a profession will continue to improve screening, diagnosis, and treatment of mental health conditions in this incredibly vulnerable population.

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Editorial

Psilocybin Therapy- A Breakthrough Alternative to SSRIs for Depression

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CONFLICTS OF INTEREST STATEMENT

None of the above authors have any conflicts of interest to report regarding this case report.

ABSTRACT

Editorial on the use of psilocybin for depression treatment.

Keywords: psilocybin, SSRIs, depression

The study *Reduced Brain Responsiveness to Emotional Stimuli With Escitalopram But Not Psilocybin Therapy for Depression* (Wall et al., 2025), published in the *American Journal of Psychiatry*, offers a compelling comparison of psilocybin therapy and escitalopram, a selective serotonin reuptake inhibitor (SSRI), in treating major depressive disorder (MDD). Using functional MRI (fMRI) to measure blood-oxygen-level-dependent (BOLD) signals, this randomized controlled trial highlights divergent effects on emotional processing. The findings reveal significant drawbacks of SSRIs, particularly their side effects, while showcasing psilocybin's potential as a transformative treatment. When paired with insights from *A Critical Evaluation of QIDS-SR-16 Using Data from a Trial of Psilocybin Therapy Versus Escitalopram Treatment for Depression* (Weiss et al., 2023), psilocybin emerges as a superior option, offering fewer side effects and a streamlined dosing schedule.

Decoding BOLD Imaging for Everyone

BOLD imaging, used in fMRI scans, is like a window into brain activity. Picture your brain as a network of regions that "light up" when you experience emotions or thoughts. When a region, such as the amygdala (linked to fear responses), is active, it demands more oxygen-rich blood. BOLD imaging tracks these blood flow changes, creating a visual map of which brain areas are working hardest. In this study, BOLD signals showed how emotional face stimuli (happy, fearful, neutral) activated brain regions before and after treatment, revealing how escitalopram and psilocybin reshape emotional responses.

Major Findings: Escitalopram vs. Psilocybin

The trial compared two MDD groups: one received two 25-mg psilocybin doses (with placebo capsules) three weeks apart, while the other took daily escitalopram (10–20 mg) for six weeks plus two 1-mg psilocybin doses (a non-active placebo). Both groups had equal psychological support. The results highlighted critical differences:

- **Escitalopram Reduced Emotional Responsiveness**: After six weeks, the escitalopram group displayed significantly lower BOLD responses to emotional faces (fearful, happy, neutral) in regions like the dorsolateral prefrontal cortex and insula. The amygdala, vital for fear processing, showed reduced activity, especially for fearful faces, consistent with *emotional blunting*—a common SSRI side effect impacting about half of users (Goodwin et al., 2017). Patients scored lower on the Laukes Emotional Intensity Scale (LEIS), reflecting a dulled emotional experience. Escitalopram also increased sexual dysfunction, as shown by elevated Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ) scores, a frequent SSRI issue affecting libido and sexual performance (Cascade et al., 2009). Notably, the reduced amygdala activity may explain why SSRIs are often more effective for anxiety disorders than depression. Anxiety conditions, like generalized anxiety disorder, are linked to heightened amygdala reactivity to threat stimuli. By dampening this response, SSRIs can reduce excessive fear and worry, providing targeted relief for anxiety symptoms (Sheline et al., 2001). However, this same blunting may hinder emotional engagement in depression, where reconnecting with emotions is therapeutic.
- **Psilocybin Maintained Emotional Vitality**: Conversely, the psilocybin group showed little change in BOLD responses, with a slight uptick for neutral faces. Amygdala activity remained stable, indicating that psilocybin preserves emotional processing. Higher LEIS scores suggested increased emotional intensity, and lower PRSexDQ scores indicated minimal sexual dysfunction. Despite significant reductions in depressive symptoms (assessed via the Quick Inventory of Depressive Symptomatology, QIDS-SR-16), psilocybin achieved these results with only two doses, contrasting with escitalopram's daily intake.

These outcomes suggest distinct neural pathways. SSRIs increase serotonin through reuptake inhibition, potentially over-activating inhibitory 5-HT1A receptors in limbic areas, causing emotional and sexual side effects (Carhart-Harris & Nutt, 2017). Psilocybin, acting as a 5-HT2A receptor agonist, enhances cortical plasticity and emotional reconnection, avoiding these drawbacks (Carhart-Harris et al., 2023).

QIDS-SR-16 Analysis Bolsters Psilocybin's Case

Weiss et al. (2023) critique the QIDS-SR-16, used in the original trial (Carhart-Harris et al., 2021), revealing its limitations in capturing psilocybin's benefits. The QIDS-SR-16's compound items (e.g., merging insomnia and hypersomnia) and sum-scoring obscure improvements in specific symptoms. The analysis showed psilocybin outperformed escitalopram in areas like energy, libido, and anhedonia—key to quality of life but underemphasized in QIDS-SR-16. Psilocybin excelled in reducing *depressed mood* and *anhedonia*, among the most debilitating depression

facets (Fried et al., 2016a), suggesting its advantages may be undervalued by broad scales like QIDS-SR-16.

Study Critiques and Limitations

The study, while robust, has caveats. The design was slightly asymmetrical: the escitalopram group received 1-mg psilocybin doses, while the psilocybin group had no escitalopram exposure, though 1-mg psilocybin lacks psychoactive effects (Madsen et al., 2019). Posttreatment fMRI scans, conducted hours after the last escitalopram dose but three weeks after psilocybin, may have missed psilocybin's acute neural impacts, as prior research noted increased amygdala activity one day post-dose (Carhart-Harris et al., 2017). The passive-viewing fMRI task may have been less sensitive than active paradigms. Functional unblinding, where psilocybin's psychoactive effects may reveal treatment allocation, is a concern, though expectancy did not significantly influence outcomes (Szigeti et al., 2022). The small sample (21 escitalopram, 25 psilocybin) and COVID-19-related dropouts call for larger trials.

Why Psilocybin Outshines SSRIs

Psilocybin and classical psychedelics offer substantial advantages over SSRIs for MDD. Unlike SSRIs, which require daily dosing for 4–8 weeks with moderate efficacy (Cipriani et al., 2018), psilocybin delivers powerful antidepressant effects with just 2–3 doses weeks apart, easing patient burden and boosting compliance. Its rapid action, often within days (Carhart-Harris et al., 2016), contrasts with SSRIs' delayed onset. Critically, psilocybin avoids SSRIs' burdensome side effects. Emotional blunting, which can impede emotional recovery, is absent; instead, psilocybin fosters emotional engagement (Roseman et al., 2019). Sexual dysfunction, a leading cause of SSRI discontinuation (Cascade et al., 2009), is significantly reduced, as PRSexDQ data confirm.

Psilocybin's 5-HT2A receptor-driven neuroplasticity creates a window for psychological growth, amplified by therapy (Carhart-Harris et al., 2023), unlike SSRIs' reliance on chronic serotonin modulation, which often sacrifices emotional and sexual health. Weiss et al. (2023) highlight psilocybin's edge in tackling core symptoms like anhedonia, offering a more comprehensive recovery.

CONCLUSION

Wall et al. (2025), supported by Weiss et al. (2023), signal a paradigm shift in depression care. Psilocybin therapy, with its minimal dosing, preserved emotional and sexual function, and potent antidepressant effects, surpasses SSRIs. While larger studies are needed to refine protocols, psilocybin's promise is undeniable, offering a future where depression treatment is both effective and life-enhancing.

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Review

Psilocybin-Assisted Therapy for Obsessive-Compulsive Disorder: A review

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CONFLICTS OF INTEREST STATEMENT

None of the above authors have any conflicts of interest to report regarding this case series.

ABSTRACT

Obsessive-Compulsive Disorder (OCD) remains a debilitating psychiatric condition with often unsatisfactory responses to current therapies. Recent research has rekindled interest in the use of classic psychedelics such as psilocybin as a novel treatment modality. This review summarizes the most current data from case reports, clinical trials, and neurobiological models to evaluate the mechanisms, efficacy, safety, and feasibility of psilocybin-assisted psychotherapy for OCD. Preliminary evidence suggests that psilocybin use in a controlled and supportive setting can produce rapid and sustained reduction in symptom burden. The putative mechanism of action is theorized to occur through the modulation of serotonin transmission, ridged thought patterns, neuroplasticity, and dysfunctional neural circuitry. Research is currently limited, and further large-scale, randomized control trials are necessary to establish the safety and efficacy of psilocybin for OCD and optimize protocols for use in conjunction with psychotherapeutic strategies.

Keywords: psilocybin, obsessive compulsive disorder, serotonin, neuroplasticity

Introduction:

OCD is characterized by the presence of recurrent and intrusive ideas, images, or urges (obsessions) and/or repetitive, rigid mental acts (compulsions) often performed in response to obsessions. This condition is associated with high levels of social and occupational impairment and a 12-month prevalence of 1.2% in the United States, being categorized as the 10th leading cause of disability among all health conditions [1-2]. Although SSRIs remain the first-line pharmacotherapy for OCD, up to 40-60% of patients do not have a satisfactory outcome, often with incomplete response and failure to achieve remission [3-4].

Thus, there is interest in alternative interventions and novel mechanisms that offer greater efficacy and better tolerability, particularly for cases that are treatment-resistant. With the recent resurgence of interest in classic psychedelics, psilocybin has resurfaced as a promising modality. Studies have been conducted on several psychiatric conditions to support the use of psilocybin in mental health. Carhart-Harris et al. [5] reported that two doses of psilocybin (10 mg and 25 mg) led to a significant reduction in depressive symptoms lasting up to three months for individuals with treatment-resistant major depression. Similar benefits have been observed in individuals with depression and anxiety symptoms associated with life-threatening illness, where administration of psilocybin led to significant improvements in mood and existential distress.

Psilocybin has also been associated with improved outcomes for individuals with substance use disorders. Johnson et al. [6] conducted an open-label trial in individuals with tobacco dependence and found abstinence rates of 80% at 6-month follow-up, higher than results observed with typical therapies (<35%). Reductions in problematic alcohol use have been observed with psilocybin-assisted therapy, where the effect was largely maintained at 3 months [7].

Such findings support the trans-diagnostic utility of psilocybin in the treatment of several core features of psychiatric disorders, including rigid thought patterns and dysfunctional self-referential processing. These alterations are critically important in OCD, a condition marked by impairment in memory, cognitive flexibility, and response inhibition [8] . Thus, this review summarizes current knowledge on the clinical application of psilocybin-assisted therapy in OCD with a focus on proposed neurobiological mechanisms, psychological impact, safety, and future considerations for research.

Neurobiological Mechanisms of Psilocybin in OCD

Psilocybin is a tryptamine alkaloid prodrug derived from Psilocybe mushrooms that are actively metabolized into psilocin following ingestion. It primarily acts as a 5-HT2A receptor partial agonist with high affinity for the 5-HT2A subtype. Activity at these receptors potentiates a molecular cascade with a multitude of effects that appear to disrupt the dysfunctional neural circuitry associated with OCD.

Task-based studies have consistently demonstrated a wide range of cognitive deficits and cognitive inflexibility in individuals with OCD, including impairment in motor response inhibition and attentional set-shifting [9-10] . Although there is no current data on psilocybin effects on cognitive testing in OCD populations, Doss et al. [11] demonstrated improved set-shifting performance in individuals with depression following psilocybin administration, indicating improvement in perseverative errors.

The Cortico-Striatal-Thalamo-Cortical (CSTC) circuitry is highly recognized for its central role in the pathophysiology of OCD. These circuits form a loop that connects the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), striatum, and thalamus. Hyperactivity in this circuitry is observed in individuals with OCD, which is theorized to lead to the strengthening of compulsive urges [12]. Disruption of such circuitry may offer a reduction in rigid and compulsive thought patterns, thereby promoting increased cognitive flexibility in individuals with OCD.

The Default Mode Network (DMN) is most active in a resting state during internally

focused thought, such as self-referential processing and rumination. Hyperconnectivity and disrupted activity with the DMN have been observed in individuals with OCD, which may facilitate the repetitive thought patterns observed in OCD. Reduced connectivity in the DMN, particularly between the medial prefrontal cortex (mPFC) and posterior cingulate cortex (PCC), has been observed following psilocybin use in healthy controls which may reduce rigid, self-referential thought patterns and alter the processing of external stimuli [13].

Clinical Study of Psilocybin and Psilocybin-assisted therapy in OCD

As with other psychiatric illnesses, clinical research into psilocybin for OCD is still in its infancy. Moreno et al. [14] was the first documented formal trial to study the use of psilocybin in OCD. Nine study participants with treatment-resistant OCD received four psilocybin doses ranging from 0.1-0.3 mg/kg in addition to non-directed therapy in a controlled setting. An acute reduction in symptoms was observed in all participants, ranging from 23% to 100%, with one participant achieving complete symptom remission at six months. No serious adverse events occurred, with transient hypertension noted in one participant.

More recently, one case report describes an individual with severe, treatment-resistant OCD who experienced dramatic symptom relief following ingestion of a single 0.25 mg/kg dose of psilocybin as an early participant in a double-blinded, randomized placebo-controlled trial [15]. The participant's Y-BOCS score declined from 24 to 0-2 over several weeks and sustained a reduction for over one year.

With the increased interest in psychedelic studies, several ongoing studies are analyzing the effects of psilocybin on OCD. Ching et al. [16] published the study protocol for a randomized, double-blind, non-crossover design comparing a single dose of psilocybin (0.25 mg/kg) to an active placebo (niacin 250 mg). Preliminary findings indicate at least a 35% reduction in symptoms at 48 hours post-treatment for those who received psilocybin, with participants expressing interest in a higher fixed dose and a second dose to achieve greater benefits and expand upon their perceived benefits, respectively. Thus, a randomized, waitlist-controlled trial with two doses of psilocybin (25 up to 30 mg) paired with non-directive support to be followed twelve months post-dosing [17] (Ching, et al., 2024). More recently, the PsilOCD trial study protocol was published, which is an exploratory trial examining the impact on cognitive flexibility and neuroplasticity through 20 participants' completion of two blinded psilocybin dosing sessions (1 mg then 10 mg) in conjunction with cognitive tasks and EEG measurements [18].

Safety and Tolerability:

Psilocybin has displayed an excellent safety profile in all trials and case reports. Adverse effects are typically transient and include nausea, mild anxiety, headaches, and increased blood pressure. Notably, these adverse events have occurred with less frequency than in SSRI trials. There was no evidence to support hallucinogen persistent perception disorder in screened participants with psilocybin when administered in a controlled setting. Importantly, careful screening was performed in all trials to exclude

individuals with any personal or close family history of psychotic symptoms. Should psilocybin gain increased support for psychiatric use, clear guidelines and therapist training pathways will be paramount in ensuring safe practice going forward.

Current limitations:

Although preliminary data suggests the utility of psilocybin in treating OCD, sample sizes are small, and the quality of evidence is low, as most studies have used an open-label or uncontrolled design. Long-term follow-up data is limited, and significant heterogeneity exists among treatment protocols, including dosing size, frequency, outcome measures, and follow-up timeframe. Additionally, psilocybin remains classified as a Schedule I substance and thus requires strict regulatory oversight.

Future considerations:

Psychedelic research remains largely in its infancy stages, and higher-quality studies are needed to determine clinically meaningful effects in this patient population. Comparative studies will be necessary to evaluate the presence or absence of dose-dependent effects and responses compared to standard treatments. Once these variables are better elucidated, the integration of psilocybin administration with current psychotherapeutic strategies is an intuitive next step, although it has practical limitations in resource-limited areas. Current studies are incorporating additional assessment modalities, including neuroimaging, cognitive assessments, and biomarkers to aid in understanding the underlying treatment mechanisms.

Conclusion:

Psilocybin represents a modality with the capacity to offer novel effects for OCD treatment where current interventions fall short. While much of the data is limited in scope, it encourages continued exploration and investment in psilocybin research. Should psilocybin prove to be clinically and meaningfully effective, the development of treatment manuals and clinical training programs will be imperative for facilitating appropriate implementation.

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Original Research

Sirolimus Augmentation of Esketamine Treatment in Treatment-Resistant Depression: A Pilot Evaluation

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CONFLICTS OF INTEREST STATEMENT

None of the above authors have any conflicts of interest to report regarding this case report.

ABSTRACT

This pilot study investigated whether oral sirolimus augments the antidepressant effects of intranasal esketamine in patients with treatment-resistant depression (TRD) unresponsive to esketamine alone. Patients received sirolimus 6 mg orally two hours prior to esketamine treatment for two treatments, taken 28 days apart. Depression severity was assessed using the MADRS, PHQ-9, and HAM-D scales at baseline, 8-, and 16-week intervals. Two-tailed t-tests showed directionally favorable but non-significant improvements at 8 weeks and 16 weeks. One-tailed t-tests, justified by a directional hypothesis, indicated significant improvements at 8 weeks. Despite significant limitations, these findings suggest that sirolimus may enhance esketamine's short-term antidepressant effects, consistent with prior studies indicating that mTORC1 modulation prolongs ketamine's therapeutic benefits. A larger, randomized controlled trial is needed to confirm these preliminary results.

Keywords: sirolimus, esketamine, treatment-resistant depression

INTRODUCTION

Ketamine has emerged as a rapid-acting antidepressant medication, providing symptomatic relief of depression-related symptoms for many patients with treatment-resistant depression (TRD). The S-enantiomer of ketamine, esketamine, has been approved for the treatment of TRD and for acute suicidal ideation, expanding therapeutic options for patients who are unresponsive to traditional antidepressant medications. Despite its efficacy, the durability of ketamine's antidepressant effects remains limited, often waning within weeks of administration and requiring ongoing maintenance therapy for sustained symptomatic relief [1].

Preclinical studies have identified activation of the mechanistic target of rapamycin complex 1 (mTORC1) as a key downstream pathway involved in ketamine's mechanism of action in depression, putatively by the induction of prefrontal glutamate neurotransmission, leading to activation of synaptic alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid glutamate (AMPA) receptors, subsequent increases in brain- derived neurotrophic factor (BDNF) levels, TrkB receptor stimulation, and mTORC1 activation, ultimately resulting in increased synaptogenesis with accompanying cognitive and behavioral adaptions in the setting of TRD [2, 3].

Despite this uneasy consensus, prior studies represent a range of conflicting findings across treatment modalities (e.g., IV or intra-cortical ketamine, intranasal esketamine) and in vivo settings (rodent models, human patients). For example, initial rodent studies found that intra-cortical inhibition of mTORC1 via sirolimus blocked ketamine's antidepressant-like effects [4]. However, a recent human study by Abdallah et al. [2] demonstrated that pre-treatment with oral sirolimus did not attenuate ketamine's effects but instead prolonged its antidepressant benefits. Further investigation by Averill et al. [5] corroborated these findings but found no effect of sirolimus on ketamine's anti-suicidal effects, suggesting a possible mechanistic divergence between ketamine's antidepressant and anti-suicidal actions.

Given these findings, we sought to investigate whether sirolimus augmentation of esketamine would enhance and/or prolong antidepressant effects in patients with TRD who had not previously responded to esketamine therapy alone. In this study, we contribute to the existing discourse by testing a novel combination of intranasal esketamine (as against other formulations) augmented by oral sirolimus, a combination that has not, to our knowledge, been represented in the existing literature.

METHODS

Study Design:

This was a retrospective per protocol chart review consisting of 18 patients diagnosed with TRD. Patients took sirolimus 6 mg orally two hours prior to scheduled esketamine treatment. Sirolimus was taken for two doses 28 days apart. Patients were eligible for this study if they had not achieved remission or relapsed into a major depressive episode (by DSM-5-TR criteria) despite ongoing maintenance therapy with intranasal esketamine. There were no limitations ion the number, frequency, nor dosing of maintenance esketamine treatments, nor on additional treatments beyond esketamine.

Outcomes:

Depression severity was evaluated using three validated scales: the Montgomery-Åsberg Depression Rating Scale (MADRS), the Patient Health Questionnaire-9 (PHQ-9), and the Hamilton Depression Rating Scale (HAM-D). Scores were collected for the treatment group at baseline (immediately prior to the first sirolimus-augmented esketamine dose), and at 8- and 16-week time points shortly prior to esketamine treatment.

Statistics:

We employed paired-sample t-tests comparing baseline scores to 8-week and 16-

week follow-up scores. Both two-tailed and one-tailed t-tests were performed. The one-tailed analysis could be justified based on a review of current literature, which supports an a priori directional hypothesis that sirolimus enhances esketamine's antidepressant efficacy. Effect sizes were calculated using Cohen's d. Statistical significance was defined as $p < 0.05$.

RESULTS

Following a two-tailed t-test analysis, none of the results met conventional thresholds for statistical significance, although all showed directionally favorable changes and moderate effect sizes (Figure 1). At 8 weeks: MADRS: Mean change −6.39 ($p = 0.053$), Cohen's $d = 0.49$; PHQ-9: Mean change −2.83 ($p = 0.066$), $d = 0.46$; HAM-D: Mean change −2.78 ($p = 0.063$), $d = 0.46$. At 16 weeks: MADRS: −4.22 ($p = 0.19$), $d = 0.32$; PHQ-9: −2.28 ($p = 0.16$), $d = 0.35$; HAM-D: −2.56 ($p = 0.099$), $d = 0.41$. See Table 1 for summary statistics.

By one-tailed analysis, results suggest that sirolimus augmentation may provide short-term clinical benefits in TRD when combined with esketamine. At 8 weeks: MADRS: $p = 0.0265$ (significant); PHQ-9: $p = 0.033$ (significant); HAM-D: $p = 0.0315$ (significant). At 16 weeks: MADRS: $p = 0.095$ (not significant); PHQ-9: $p = 0.08$ (not significant); HAM-D: $p = 0.0495$ (marginally significant). See Table 2 for summary statistics using a one-tailed analysis.

Figure 1

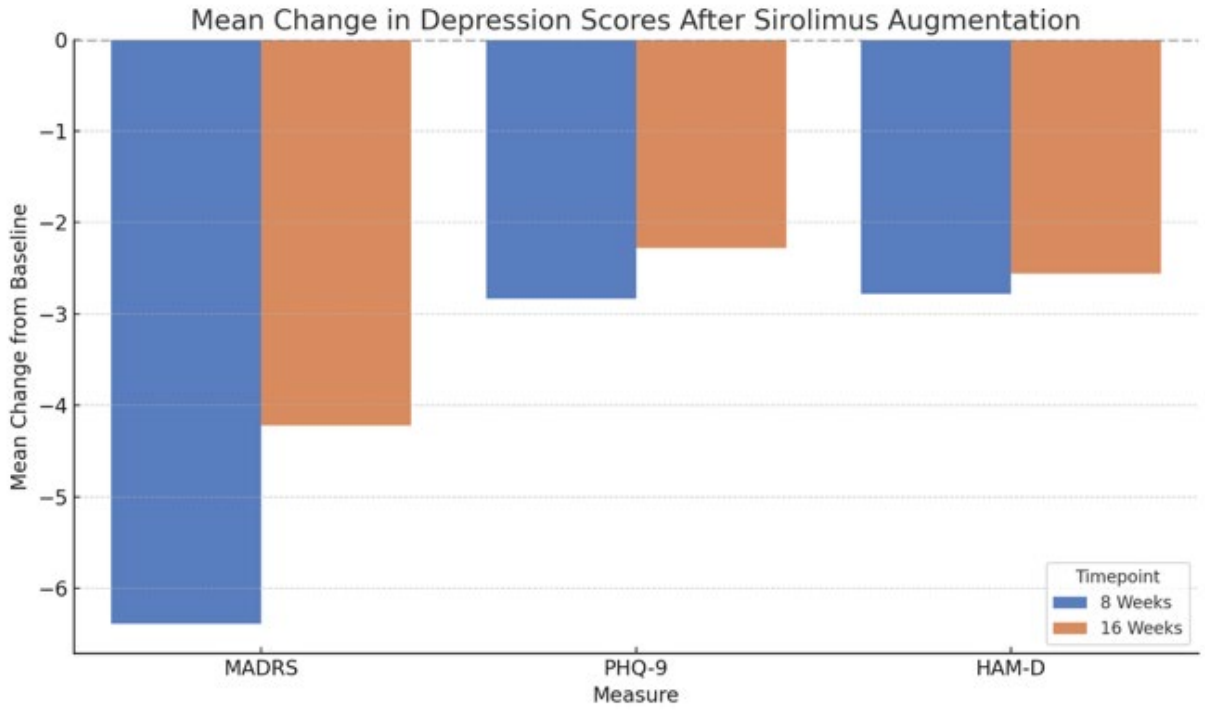

Table 1

8 Weeks	Mean Δ [95% CI]	p-value	Cohen's d	t-statistic
MADRS	-6.39 [-12.87, 0.09]	0.053	0.49	-2.08
PHQ9	-2.83 [-5.88, 0.21]	0.066	0.46	-1.96
HAM-D	-2.78 [-5.79, 0.23]	0.063	0.46	-1.95

Table 2

16 Weeks	Mean Δ [95% CI]	p-value	Cohen's d	t-statistic
MADRS	-4.22 [-10.80, 2.36]	0.19	0.32	-1.35
PHQ9	-2.28 [-5.54, 0.99]	0.16	0.35	-1.47
HAM-D	-2.56 [-5.65, 0.53]	0.099	0.41	-1.74

DISCUSSION

This pilot investigation sought to explore whether pretreatment with sirolimus could enhance the antidepressant effects of intranasal esketamine in patients with TRD. Under a two-tailed analysis, trends toward improvement were seen across all outcome measures at both 8 and 16 weeks, although results did not reach statistical significance. When an a priori directional hypothesis was considered, a one-tailed analysis demonstrated significant improvement at 8 weeks on all three measures.

These findings, and the justification of a one-tailed t-test, as warranted by a prior directional hypothesis, are consistent with the prior work by Abdallah et al. [2] and others [5], which found a prolonged antidepressant effect of ketamine following sirolimus pretreatment in humans, and support the potential of mTORC1 modulation to sustain ketamine's therapeutic impact. The present results extend this possibility to esketamine, a more accessible and widely used (in this case, intranasal) treatment modality.

However, several methodological limitations must be considered. This per -protocol study was significantly underpowered (estimated power ~0.13), limiting our ability to detect small -to -moderate effects with confidence. The absence of randomization and placebo control introduces bias and limits causal inference. Differences in esketamine dosing frequency compared to IV ketamine protocols used in earlier research may have also masked potential effects. Additionally, differences in delivery route (nasal vs. intravenous) may alter pharmacodynamics and influence the interaction of these medications with sirolimus. Finally, justification of a one-tailed t-test as warranted by an a priori directional hypothesis is itself based on a literature with mixed results concerning the effects of sirolimus, and animal studies have showned that intracerebroventricular injection of sirolimus effectively blocked ketamine-induced synaptogenesis and behavioral responses that were taken to represent antidepressant effects in rodent models of depression [4].

In spite of these limitations, this exploratory analysis suggests the potential for sirolimus as an adjunct to esketamine-based therapy in TRD. No doubt, a larger, randomized controlled trial is warranted to confirm these preliminary findings.

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