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COMBINATION OF PSILOCYBIN AND COGNITIVE BEHAVIORAL THERAPY IMPROVES OXYTOCIN LEVELS AND DEPRESSIVE SYMPTOMS IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER

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ABSTRACT

Background: Major depressive disorder is a prevalent psychological condition that is characterized by sustained low mood, dysfunction and biological dysregulation. Depression can be treated with cognitive behavioral therapy, and newer studies indicate that psilocybin-based therapy may improve depressive symptoms when used under supervised psychological support**.** Oxytocin, a neuropeptide that plays a role in stress, emotions and bonding, may help us understand treatment effects.

Objective: To evaluate the effect of psilocybin therapy, cognitive behavioral therapy, and combined psilocybin assisted cognitive behavioral therapy on depressive symptoms and serum oxytocin levels among patients with major depressive disorder.

Methods: This randomized controlled trial was carried out at the Psychiatry Department of Hayatabad Medical Complex and Khyber Medical University, Peshawar from 1st December 2024 to 30th July 2025. Sixty-seven patients with major depressive disorder were included and randomly distributed into four groups: 'SSRI treatment, CBT, psilocybin therapy, and psilocybin combined with CBT'. Hamilton Depression Rating Scale was used to measure the severity of depression at baseline, week 6 and week 10. Serum oxytocin levels were also evaluated. Data was analyzed using SPSS 25. Repeated-measures ANOVA, Bonferroni post hoc comparisons were applied.

Results: The control group showed minimal change in HAM-D scores, while marked reductions were observed in all active intervention groups. By week 10, mean HAM-D scores decreased to 2.84 ± 2.01 in the CBT group, 3.24 ± 1.56 in the psilocybin group, and 2.50 ± 1.51 in the psilocybin assisted CBT group. Repeated-measures ANOVA showed a significant effect of time on HAM-D scores and a significant time × group interaction ($p<0.001$). Serum oxytocin levels increased in CBT, psilocybin, and combined treatment groups, with the greatest rise being observed in the psilocybin assisted CBT. Between-group differences in oxytocin were 'not significant' ($p=0.649$), but significant rises were observed within all intervention groups.

Conclusion: Patients treated with psilocybin, CBT, or their combined approach showed significant improvement in depressive symptom**s.** Serum oxytocin levels increased most significantly in the combined treatment group, suggesting a possible neurobiological role of oxytocin in treatment response.

KEYWORDS: Major depressive disorder; Psilocybin; Cognitive behavioral therapy; Oxytocin; HAM-D; Depression, SSRI (selective serotonin re-uptake inhibitors)

INTRODUCTION

Major depressive disorder (MDD) is a prevalent psychiatric illness featuring persistent depressed mood, anhedonia, cognitive impairment, appetite and sleep disturbances, functional impairment, and a decrease in quality of life. Although antidepressant drugs and psychological therapies are available, many patients still suffer from suboptimal response, recurrence, residual symptoms or resistance to treatment (1). Traditional antidepressant treatment typically takes weeks to have an effect and may not effectively target emotional processing, social isolation, interpersonal impairment and neurobiological dysregulation implicated in depression. Thus, novel treatments that integrate psychological and biological processes are being investigated for the treatment of MDD (2).

Cognitive behavioral therapy (CBT) is a well-established psychological treatment for depression. It involves the recognition and change of dysfunctional thoughts, the alteration of negative cognitive biases, the enhancement of coping skills and the promotion of a more active and engaged lifestyle (3). While recent evidence indicates that CBT is effective in reducing symptoms of depression, both as a stand-alone treatment and combined with medication, some patients still fail to respond to CBT and the success of treatment may require motivation, engagement, cognitive flexibility, and emotional processing skills. Keeping this in mind, integrated treatment approaches that increase emotional openness and responsiveness to therapy are receiving increasing attention (4).

Psilocybin-assisted CBT is a new approach to treating depression. Psilocybin is a serotonergic psychedelic that may affect mood, emotional processing, psychological flexibility, and interpersonal connectedness when used in a therapeutic setting. Randomized controlled trials and follow-up research have shown that psilocybin-assisted therapy quickly and persistently reduces depression symptoms in people with MDD and treatment-resistant depression (2, 5, 6). These results indicate that psilocybin may offer therapeutic benefits beyond traditional antidepressant mechanisms, particularly when administered with psychological preparation, support and integration.

Oxytocin is a neuropeptide hormone that plays a role in bonding, emotion, stress, attachment, trust, and social interactions. Oxytocin dysfunction has been found in depression and anxiety-related disorders, which suggests that oxytocin may be associated with emotional symptoms and interpersonal processes (7). Given that CBT and psilocybin-assisted CBT may impact emotional processing and interpersonal connectedness, serum oxytocin may be a valuable biological indicator of treatment effects. Therefore, this study was conducted to evaluate changes in depressive symptoms and serum oxytocin levels among patients with MDD treated with conventional therapy, CBT, psilocybin, and combined psilocybin assisted CBT.

MATERIALS AND METHODS

The present randomized controlled trial aimed to evaluate the comparative effects of conventional treatment, cognitive behavioral therapy, psilocybin therapy, and psilocybin-assisted cognitive behavioral therapy on depressive symptoms and serum oxytocin levels in patients with major depressive disorder measured by the Hamilton Depression Rating Scale (HAM-D) in patients with MDD (ClinicalTrials.gov ID: NCT06746441). It was conducted at the Psychiatry Department of Hayatabad Medical Complex and Khyber Medical University, Peshawar. Biochemical analysis was carried out at Khyber Medical University laboratories from 1st December 2024 to 30th July 2025. Approval for the study was taken from Ethical Review Committee of Khyber Medical University, Peshawar (NO-KMU/IBMS/IREB/11th meeting/2024/215-AB on 03.09.2024, No.DIR/KMU/-AS&RB/IP/OO2870, 158th meeting on 27.07.2024), and written consent from the Psychiatry Department of Hayatabad Medical Complex (Approval No: 2028 on 09.09.2024). Informed consent was also obtained from all participants.

We used mean ± SE (n=300) values of HAM-D from Asghar et. al.(8) Standard deviation (SD) was calculated as SD = SE*√n.

Group	Baseline (SD)	6 Weeks (SD)	12 Weeks (SD)
Group 1	22.9 (10.39)	14.9 (13.86)	8.5 (8.66)
Group 2	21.9 (10.39)	15.2 (10.39)	11.4 (13.86)

Pooled SD = 11.42 and Effect size= 0.45. For a design with 4 groups and 3 measurements (time points), we used G Power with power 80%, α= 0.05 and '95% confidence level, sample size was calculated as 20 (5 per group)'. If considering medium effect size of 0.25, sample size would be 13 per group. Adjusting for attrition, we included 60 participants (15 participants in each of the four groups). However, due to dropouts in the intervention groups, we recruited 20 participants in each intervention group. The final analyzed sample included 67 participants, distributed as 15 in the control group, 19 in the CBT group, 17 in the psilocybin group, and 16 in the psilocybin plus CBT group. Participants were selected using a purposive non-probability sampling technique. 'We included male and female patients between the ages of 18 to 50 years who had a diagnosis of MDD according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria and were experiencing active depressive symptoms (i.e. a score of greater than 16 on the HAM - D during the past 14 days)' Subjects were excluded if they had a resting systolic blood pressure of 140 mmHg or greater and a diastolic blood pressure of 90 mmHg or greater, were taking more than one selective serotonin reuptake inhibitor (SSRI) drug, had another concurrent psychiatric disorder, had a suicidal risk with a score of 3 or greater on item 3 of the HAM-D, had taken psychedelic drugs or ketamine in the past 12 months, were pregnant or breastfeeding, had a history of substance abuse or alcohol intake in the past six months, had cardiovascular disease, stroke, transient ischemic attack, epilepsy, seizures, or diabetes mellitus.

Participants were screened and those who provided informed written consent were assigned to one of four groups by lottery method. The control group received traditional antidepressant treatment with SSRI. The CBT group were given cognitive behavioral therapy. The psilocybin group received psilocybin therapy. The group receiving psilocybin assisted CBT received psilocybin and CBT.

The CBT and psilocybin assisted CBT groups received scheduled CBT sessions every week for 8 to 10 weeks (protocol was for 10 weeks but some participants took 8 sessions; and were included in analysis). These sessions were 50-60 minutes long and were delivered by certified CBT therapists. The CBT program included discussion of difficult life events, identification of negative beliefs and thoughts, challenging of distorted thinking, cognitive restructuring, behavioral activation, review of homework, and encouragement of positive coping strategies. Prior to starting CBT, depression severity was measured by HAM-D scale.

Study participants in the psilocybin and psilocybin assisted CBT groups received psilocybin therapy in a dose of 7 grams first at baseline and subsequently after 06 weeks (2^{nd} dose of 7 grams) in the presence of trained clinicians. The sessions were held in a quiet and safe environment and participants were watched for psychological and clinical safety. Blood pressure, heart rate and oxygen saturation levels were monitored throughout the session. Anxiety and mood were monitored as well. Antiemetic medications were administered as needed. Discharge was only carried out when the effects had worn off, participants were stable and willing/confident to go home. Adverse Event (AE) reporting form was filled by the attending investigator after discussion with Participant/accompanying attendant, and submitted for record.

A questionnaire was administered to gather sociodemographic data, such as age, gender, education level, socioeconomic background and other relevant medical history. The HAM- D Scale was used to measure the severity of depression at baseline, week 6 and week 10. Serum oxytocin concentrations were also assessed at the same time intervals.

Biochemical assessment was done by obtaining 5 ml of early morning venous blood of each participant at baseline, week 6 and week 10. 5 mL blood was drawn into gel separator tubes for serum. Serum samples in the gel tubes were left 'to clot at room temperature for 30 minutes, and centrifuged at 3000 rpm for 10 to 15 minutes' The supernatant was stored in appropriately labeled Eppendorf tubes at -80°C until determination of serum oxytocin by ELISA.

Data was analyzed using SPSS version 25. Continuous variables such as age, HAM-D scores, and serum oxytocin levels were presented as mean ± standard deviation. Categorical variables such as sex and treatment group were presented as frequency and percentage. Repeated-measures ANOVA was applied to compare changes in HAM-D scores and serum oxytocin levels across the three time points and among treatment groups. Bonferroni-adjusted pairwise comparisons were used for time-wise comparisons. Pearson correlation was used to check association of change in HAM-D scores with change in oxytocin levels. Results with $p<0.05$ were treated as statistically significant.

RESULTS

A total of 67 patients with MDD were included. The largest group was the CBT group (n=19), followed by the psilocybin group (n=17), psilocybin assisted CBT group (n=16), and control group (n=15). Overall, females (n=39, 58.2%) were more than males (n=28, 41.8%).

The mean age of the groups was almost similar, with the control group having a mean ± SD age of 26.73 ± 8.05 years, Psilocybin 27.35 ± 5.45, CBT 26.84 ± 7.01 and the psilocybin assisted CBT 28.94 ± 8.90 years.

HAM-D scores did not change significantly in the control group. Marked reduction in HAM-D scores was observed in the CBT, psilocybin, and psilocybin assisted CBT groups. The lowest final HAM-D score was seen in the psilocybin assisted CBT group.

Table 1. Change in HAM-D scores across treatment groups.

	Groups			
Time point	**Control n=15**	**CBT n=19**	**Psilocybin n=17**	**Psilocybin +CBT n=16**
Baseline	18.00 ± 1.25	18.74 ± 1.88	21.18 ± 3.76	19.06 ± 2.14
Week 6	17.87 ± 1.25	6.26 ± 2.56	9.06 ± 1.34	6.81 ± 2.26
Week 10	17.93 ± 1.33	2.84 ± 2.01	3.24 ± 1.56	2.50 ± 1.51
P values				
ANOVA	0.629	<0.001	<0.001	<0.001
Baseline vs Week 6	0.589	<0.001	<0.001	<0.001
Baseline vs Week 10	0.885	<0.001	<0.001	<0.001
Week 6 vs Week 10	0.783	<0.001	<0.001	0.001

There was a statistically significant effect of time on HAM-D score, **$F=1833.842$, $p<0.001$, partial $\eta^2=0.967$**. The time × group interaction was also significant, **$F=189.804$, $p<0.001$, partial $\eta^2=0.900$**, showing that improvement in depressive symptoms differed significantly between groups. The between-subjects group effect was also significant, **$F=100.140$, $p<0.001$, partial $\eta^2=0.827$**. This means that the decreases in depression severity varied between groups.

Post hoc tests demonstrated significant decreases in the HAM-D from baseline to week 6, baseline to week 10 and week 6 to week 10 (all $p \leq 0.001$).

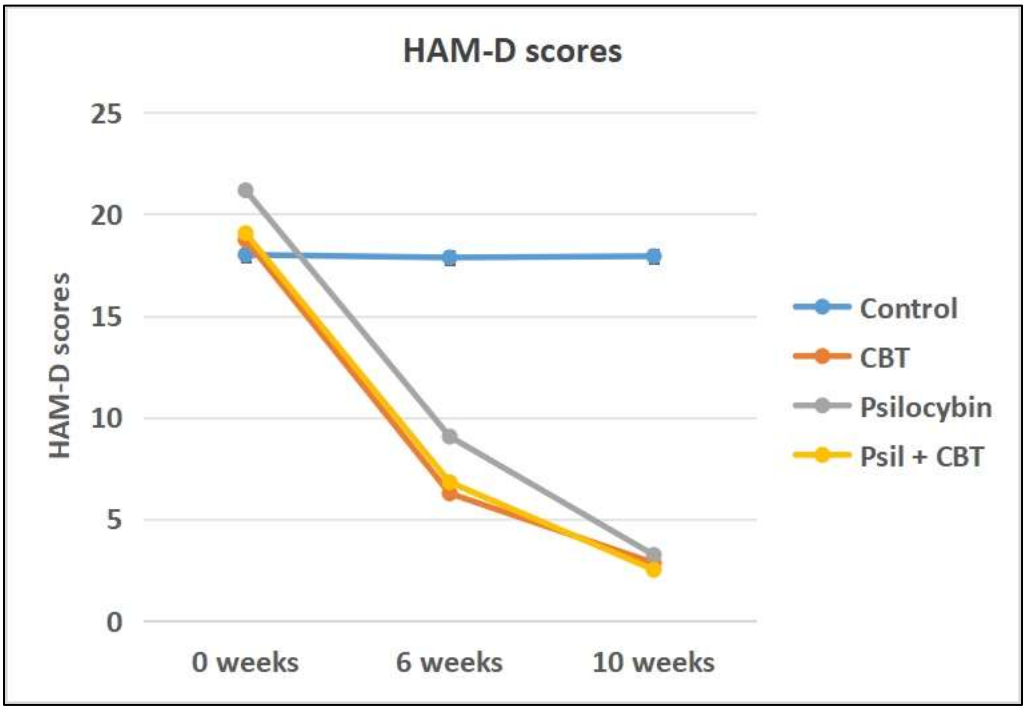

Figure 1. HAM-D scores across three time points among control and intervention groups

Figure 1 shows the HAM-D scores over time. The control group showed minimal change across the three time points, whereas CBT, psilocybin, and psilocybin assisted CBT groups demonstrated a marked reduction in depressive symptoms from baseline to week 10. The sharp decline in the intervention groups supports the significant time and time × group effects observed in repeated-measures ANOVA (Table 1).Bonferroni-correction pairwise comparisons revealed that HAM-D scores were significantly reduced from baseline to week 6, baseline to week 10 and week 6 to week 10 (Table 1).

Serum oxytocin levels showed minimal change in the control group. However, all intervention groups showed an increase in oxytocin level, with the psilocybin and CBT group showing the highest final level.

Table 2. Change in serum oxytocin levels across treatment groups

	Groups			
Time point	**Control n=15**	**CBT n=19**	**Psilocybin n=17**	**Psilocybin+ CBT n=16**
Baseline	24.90 ± 3.81	22.21 ± 5.37	21.69 ± 4.10	22.22 ± 3.32
Week 6	25.29 ± 3.39	25.28 ± 3.44	24.71 ± 2.43	25.31 ± 2.05
Week 10	25.35 ± 3.67	27.03 ± 1.93	27.21 ± 1.74	29.69 ± 2.36
	P values			
ANOVA	0.819	<0.001	<0.001	<0.001
Baseline vs Week 6	0.532	0.003	0.001	0.001
Baseline vs Week 10	0.211	0.001	<0.001	<0.001
Week 6 vs Week 10	0.864	0.033	0.001	<0.001

HAM-D scores changed significantly over time, $F=1833.842$, $p<0.001$, partial $\eta^2=0.967$. 'The significant time × group interaction, $F=189.804$, $p<0.001$, partial $\eta^2=0.900$, showed that symptom reduction followed different patterns across the treatment groups'. The between-group effect was also significant, $F=100.140$, $p<0.001$, partial $\eta^2=0.827$, suggesting that the level of improvement varied by treatment type.This means that when average oxytocin values were compared across groups, the overall group effect was not significant. However, within-group analysis showed significant improvement over time in the intervention groups (Table 2).

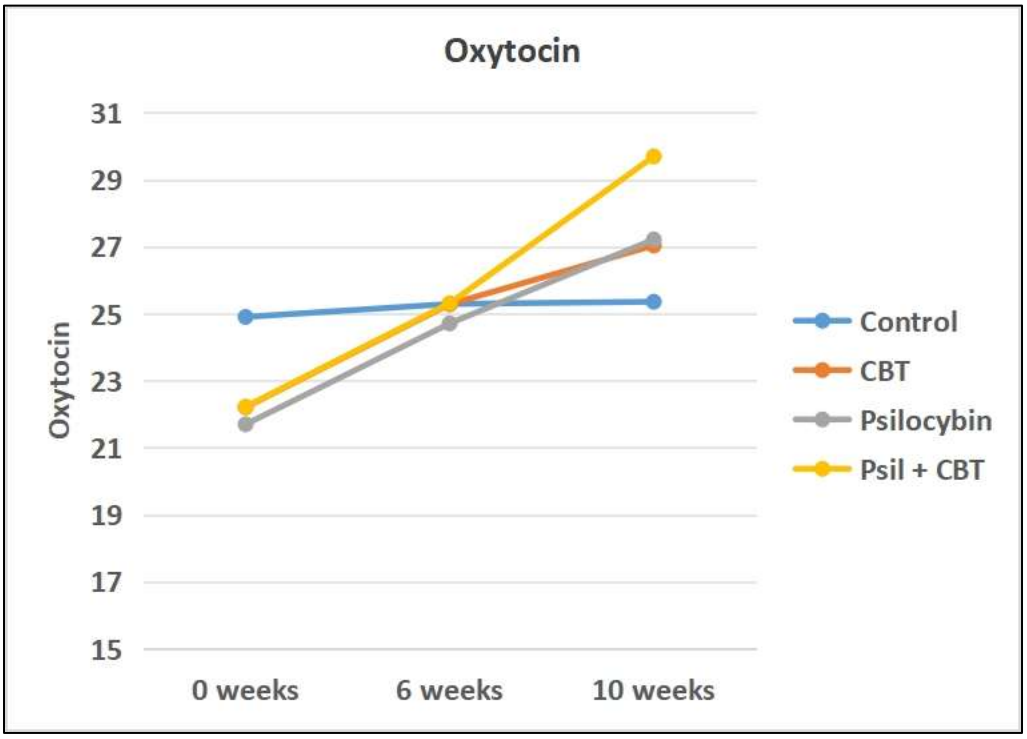

Figure 2. Oxytocin levels across three time points among control and intervention groups

Figure 2 illustrates the change in serum oxytocin levels over time. Oxytocin levels remained relatively stable in the control group, while an increasing trend was observed in the CBT, psilocybin, and psilocybin assisted CBT groups. The highest rise was observed in the combined psilocybin plus CBT group by Week 10.

The sharpest decline in HAM-D scores was in the psilocybin group (17.94), followed by psilocybin plus CBT (16.56) and CBT (15.90) groups; while the control group showed minimal improvement (0.07). Serum oxytocin increased more in the psilocybin plus CBT group (7.47) than in the psilocybin (5.52) and CBT groups (4.83). The reduction in HAM-D scores showed a 'significant inverse relationship with the rise in oxytocin levels ($r = -0.453$, $p<0.001$)'

Table 3. Mean change in HAM-D scores and oxytocin levels from baseline to Week 10

Group	HAM-D Baseline	HAM-D Week 10	Mean HAM-D Reduction	Oxytocin Baseline	Oxytocin Week 10	Mean Oxytocin Increase
Control	18.00	17.93	0.07	24.90	25.35	0.45
CBT	18.74	2.84	15.90	22.21	27.03	4.83
Psilocybin	21.18	3.24	17.94	21.69	27.21	5.52
Psilocybin + CBT	19.06	2.50	16.56	22.22	29.69	7.47

In summary, the study indicates that CBT, psilocybin and psilocybin assisted CBT led to significant reduction of depressive symptoms, with 'a significant increase in serum levels of oxytocin in the combined psilocybin' assisted CBT group.

DISCUSSION

This randomized controlled trial evaluated changes in depressive symptoms and serum oxytocin levels among patients with MDD treated with conventional therapy (SSRI), CBT, psilocybin, and combined psilocybin assisted CBT. According to the findings of this study, HAM-D scores decreased markedly in all active treatment groups, while the control group showed almost no clinical change. The highest improvement in depressive symptom was observed in the psilocybin and psilocybin assisted CBT groups, with the combined group having the lowest HAM-D score at week 10. The repeated-measures analysis demonstrated a significant time-related change and a significant time × group interaction, indicating that improvement differed across treatment arms. Serum oxytocin levels also increased in the CBT, psilocybin, and psilocybin assisted CBT groups, with the greatest increase 'in the combined intervention group, while the control group showed only minimal change' These findings suggest that symptom improvement may be accompanied by favorable neurobiological changes related to social bonding, emotional regulation, and stress modulation.

The significant decrease in HAM-D scores seen in the groups receiving psilocybin is in line with recent clinical trials that have reported rapid antidepressant effects of psilocybin-assisted therapy. Davis et al. found that psilocybin-assisted therapy induced large antidepressant effects in patients with MDD. (6). Likewise, Raison et al. reported a single 25-mg dose of psilocybin (active component) resulted in clinically significant reduction in depressive symptoms and disability in patients with MDD (9). Goodwin et al. also showed that 25 mg psilocybin was more effective in reducing depressive symptoms in treatment-resistant depression than a 1-mg control dose (10). These studies are consistent with our observations that psilocybin was associated with a marked reduction in depression scores at week 6, which improved further by week 10.

The findings of this study also suggest that structured psychotherapy improves response to treatment. The CBT group demonstrated a significant reduction in HAM-D scores, suggesting that restructuring of negative thoughts, activation of positive behaviors, and therapist-assisted change in negative thinking styles had beneficial effects on depressive symptoms. This is consistent with recent studies that have shown that CBT is one of and the most effective forms of psychotherapy for depression. Cuijpers et al. in a recent meta-analysis found that CBT compared with control conditions, and in the acute phase (but not long term) compared with pharmacotherapy, was effective (11). Similarly, Kambeitz-Ilankovic et al. found that face-to-face delivered CBT led to a large reduction in depressive symptoms (12), and Wright et al. found computer-delivered CBT with treatment as usual was superior to usual treatment for depressive symptoms (13).

The group receiving psilocybin assisted CBT had a particularly good outcome, with the lowest final HAM-D score and the greatest increase in serum oxytocin levels. The result may reflect a synergy between the effects of psilocybin to increase psychological flexibility, openness to experience and willingness to engage in therapy, together with the structured support of CBT to alter thoughts, behaviors and emotional responses. 'Carhart-Harris et al. compared psilocybin with the antidepressant escitalopram and found that both types of therapy induced antidepressant effects' but secondary outcomes were favoring psilocybin (13). More recently, Erritzoe et al. noted that psilocybin therapy and escitalopram were both associated with sustained improvement after six months, with psilocybin showing greater improvement in psychosocial functioning and connectedness (14). These findings are consistent with the idea that psilocybin may potentially facilitate interpersonal and emotional processes that may be further supported by psychotherapy.

The rise in serum oxytocin in the active treatment arms is of interest since oxytocin is related to social bonding and affiliative behavior, emotional regulation, stress response, and trust. The increase observed in its levels in the group receiving psilocybin assisted CBT may indicate that psychotherapeutic improvement may have been associated with an increase in prosocial neuroendocrine function. Tuman et al. demonstrated changes in the level of serum oxytocin in patients with depression and anxiety disorders, therefore supporting its role in affective disorders (7). Jiang et al. referred to oxytocin as a neuropeptide associated with the HPA axis, immune functions and affective disorders (15). Ellenbogen et al. also found that intranasal oxytocin, administered as an adjunct to psychotherapy for MDD, enhanced early therapeutic relationship and efficacy in a pilot randomized study (16). Though these studies are consistent with the possibility that oxytocin is involved not only in the severity of depressive symptoms but in responsiveness to psychotherapy and social-emotional improvement.

While this study demonstrated that the within-subjects factor of the repeated-measures ANOVA for oxytocin was significant, with increases within active treatment groups, but the between-subjects factor for group was not significant. . This implies that while there were increases in oxytocin over time in the CBT, psilocybin, and combined treatment groups, the average difference between groups was not sufficient to show significance. This could have been caused by group size, variation in baseline levels, variability of oxytocin in the bloodstream, and the short duration of the follow-up. Recent literature shows that oxytocin levels in people with depression do not follow a consistent trend. 'Orihashi et al. found that older adults with higher levels of depressive symptoms had lower levels of serum oxytocin' while reviews on the role of oxytocin in psychiatric disorders highlight that oxytocin may have different effects according to sex, attachment style, social environment, stress condition, as well as treatment context (17, 18). Therefore, the oxytocin findings of the present study should be interpreted as promising but preliminary. The findings may be different with more sample size or increased duration of treatment/follow-up.

The antidepressant response is also supported by systematic reviews and meta-analyses of psilocybin for depression. Haikazian et al. indicated psilocybin-assisted therapy had significant effects on depressive symptoms, response, and remission, but highlighted the need for more high-quality studies (19). Perez et al. reviewed the dose-response and reported the antidepressant effects of psilocybin-assisted therapy (20). Li et al. examined the randomized controlled studies in MDD and reported that psilocybin improved depressive symptoms in a number of trials, but also noted the need for larger and longer-term studies (21). These reviews support the clinical findings from the current study, but also highlight the need to interpret the data with caution as the research is still evolving.

Overall, this study demonstrates that psilocybin and CBT both may alleviate depressive symptoms, and that they may be particularly beneficial in improving both clinical and neurobiological indices when used together. The increased serum level of oxytocin in the combined group may suggest improved emotional bonding, social trust and stress management, which are important for recovery from depression (5). Gukasyan et al. found that the antidepressant

response to psilocybin-assisted therapy may last for up to 12 months in some patients, and recent follow-up findings from a comparison of psilocybin and escitalopram indicate that this response may extend to long-term improvement in social functioning and connectedness (22). These results are in line with the current study showing that the combination may not only reduce symptoms, but may have other effects.

Strengths of the Study

The main strengths of this study is the randomized controlled design with four experimental groups, which evaluated standard treatment, CBT, psilocybin, and psilocybin assisted CBT. HAMD scores and oxytocin levels were measured at multiple time points which enabled assessment of change rather than a one-time post-treatment evaluation. The study also included both a clinical measure (HAM-D) and a biological measure (serum oxytocin), which was able to provide both clinical and neuroendocrine context for the effect of treatment. The use of both monotherapy and combined therapy is strength of this study, as it allowed us to examine whether there are combined or synergistic effects of psilocybin and CBT.

Limitations of the Study

This study had some limitations. First, the final sample sizes were small and unequal, which might have limited statistical power, particularly in between-group oxytocin analyses. Second, the follow-up duration was limited to Week 10, so long-term durability of symptom improvement and oxytocin changes could not be assessed. Third, oxytocin is biological variable, and levels may be affected by sex, stress, attachment, sampling time, and interpersonal interactions; thus, serum oxytocin levels may not completely reflect central oxytocin levels. Fourth, blinding was challenging because psilocybin has subjective effects, which may affect patient expectancy and response. Fifth, the study involved a single clinical settings (single center study), so it may not be applicable to larger population and different areas.

CONCLUSION

Psilocybin therapy, CBT, and combined psilocybin assisted CBT were associated with significant reduction in depressive symptoms among patients with major depressive disorder. Serum oxytocin levels increased in all active treatment groups, with the greatest rise being observed in the combined psilocybin assisted CBT group. These findings suggest that combined psilocybin and CBT may provide greater clinical and neurobiological benefit than either approach alone. Larger, blinded, ‘multicenter trials with longer follow-up are recommended to confirm the durability, safety, and mechanistic role of oxytocin’ in treatment response.

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