European Journal of Clinical Pharmacy
Print ISSN: 2385-409X **Online ISSN**: Applied Website:
https://farmclin.com/

Oxytocin and Beta-endorphin levels in methamphetamine addiction and depression patient

Noor Haidar Talib1, Maysaa Jalal Majeed2 and Mahir M. Hussein3

[1]College of Pharmacy, Mustansiriyah University, Baghdad, Iraq.
noor.albayati@uomustansiriyah.edu.iq
Orcid ID: 0009-0002-5770-3260
[2]University of Baghdad, College of Medicine, Department of Biochemistry, Iraq.
maysaajmajeed@comed.uobaghdad.edu.iq
ORCID ID: 0009-0002-8884-6715
[3]Ibn-Rushed Psychiatric Teaching Hospital, Baghdad, Iraq.
dr_mahir70@yahoo.com
ORCID ID: 0000-0002-9517-5342

ABSTRACT

Background: Methamphetamine addiction and major depressive disorder are neuropsychiatric conditions characterized by disruptions in neurotransmitter systems and stress regulation. Oxytocin and beta-endorphin, neurochemicals involved in social bonding, stress response, emotional regulation and reward system, have been implicated in both disorders. Altered oxytocin or beta-endorphin signaling may contribute to the pathophysiology of addiction and depression through interaction with dopamine, serotonin, and the hypothalamic-pituitary-adrenal axis. Understanding oxytocin and beta-endorphin changes in these conditions could inform novel therapeutic approaches. **Aim**: To assess serum oxytocin levels in patients with methamphetamine addiction and depression patients compared to healthy controls, and to evaluate their potential roles in mood regulation and reward behaviors. **Methods**: This analytical observational study included 25 methamphetamine-dependent individuals, 25 patients diagnosed with depression, and 30 healthy controls, matched for age and sex. Diagnoses followed standardized psychiatric criteria. Serum oxytocin was measured using ELISA from blood samples collected, stored at -20°C, and analyzed simultaneously. Exclusion criteria included comorbid substance use disorders, hepatic, renal, or cardiac diseases. Statistical analysis employed ANOVA and Pearson correlation, with significance set at $p<0.05$. **Results**: Oxytocin and beta-endorphin levels differed significantly among the groups ($p < 0.001$), with the lowest mean levels observed in the methamphetamine group oxytocin (20.70 ± 3.16 pg/mL), beta-endorphin (23.73±4.99 ng/L) intermediate levels in the depression group oxytocin (23.19 ± 3.08 pg/mL), beta-endorphin (11.99±3.79 ng/L) and highest in controls oxytocin (40.80 ± 11.40 pg/mL), beta-endorphin (34.89±5.83 ng/L). No significant age differences were observed among groups. Positive correlation between oxytocin and beta-endorphin was also noted P-value (<0.001) in addiction and depression groups. **Conclusion**: oxytocin and beta-endorphin are significantly decreased in methamphetamine addiction and depression compared to healthy individuals, underscoring their role in the pathophysiology of both conditions. Recognizing these neurochemical alterations may facilitate the development of more effective therapies.

KEYWORDS: Addiction, beta endorphin, depression, methamphetamine, oxytocin.

How to Cite: Noor Haidar Talib, Maysaa Jalal Majeed and Mahir M. Hussein, (2026) Oxytocin and Beta-endorphin levels in methamphetamine addiction and depression patient, European Journal of Clinical Pharmacy, Vol.8, No.1, pp. 2523-2528

INTRODUCTION

Methamphetamine (MA) is well known active psychostimulant widely abused around the world that belongs to amphetamines chemical group. Prolonged use at high levels causes strong dependence(1). MA addiction in Iraq has become a significant public health and safety crisis in 2024(2). MA targets monoamine transporters, particularly dopamine (DA), norepinephrine (NE), and serotonin (5-HT), in the CNS. Its primary mechanism of action is the release of neurotransmitters from presynaptic terminals, which predominantly reverses their actions. Additionally, MA inhibits monoamine oxidase (MAO), an enzyme responsible for the breakdown of DA, NE, and 5-HT, thereby increasing their availability and enhancing their effects. The pharmacological effects of MA include increased arousal, alertness, focus, mood, sociability, and self-esteem(3).

Methamphetamine addiction involves three main stages: intoxication, marked by excessive use, intense euphoria, heightened energy, sociability, and dopamine-mediated reinforcement; withdrawal, characterized by fatigue, dysphoria, cravings, sleep disturbances, appetite changes, and psychomotor alterations lasting days to weeks, which increase relapse risk; and craving, a persistent psychological urge triggered by internal or external cues that drives relapse even after abstinence(4).

Depression is a common psychiatric disorder and a major contributor to the global burden of diseases, associated with high rates of suicidal behavior and mortality. Major depressive disorder (MDD), a main cause of disability worldwide, is characterized by physical changes such as depressed mood, tiredness, weight loss, and appetite loss.(5)

The prevalence of depression is increasing yearly. About 300 million people in the world are affected by MDD, which has become one of the main causes of disability. Pharmacological therapies for MDD can effectively control symptoms; thus, patients may experience recurrence within a short time after discontinuing medication (6). Several hypotheses explain the pathogenesis of MDD. The HPA axis dysfunction hypothesis suggests that chronic stress activates the axis, increasing glucocorticoid and cortisol levels, which can damage neurons and disrupt mood regulation. The monoamine hypothesis attributes depression to deficiencies in key neurotransmitters such as serotonin, dopamine, and norepinephrine. The inflammatory hypothesis proposes that elevated proinflammatory cytokines like IL-6 and TNF-α, along with altered levels of neurotrophic factors, contribute to neural dysfunction. Additionally, genetic variations influence individual susceptibility to MDD, affecting the biological pathways involved (7).

Depression and methamphetamine addiction share several neurobiological pathways, particularly involving disruptions in the dopamine and serotonin systems, as well as inflammatory processes in the brain (8).

Both conditions are associated with alterations in neurotransmitter levels, dysfunction of the hypothalamic–pituitary–adrenal (HPA) axis, and increased levels of pro-inflammatory cytokines, which contribute to mood dysregulation and cognitive impairment. Despite these similarities, they are distinct in their core clinical features: depression is primarily characterized by persistent low mood, loss of interest or pleasure (anhedonia), and a range of cognitive and physical symptoms (9). While methamphetamine addiction is defined by compulsive drug-seeking behavior, loss of control over use, and a cycle of intoxication, withdrawal, and craving. Furthermore, while both conditions can lead to significant disability and impaired functioning, the primary driver in depression is mood disturbance (10), whereas in methamphetamine addiction, it is the maladaptive pattern of substance use and its direct neurotoxic effects. Importantly, these disorders frequently co-occur, with each increasing the risk and severity of the other, necessitating integrated treatment approaches for optimal outcomes(11).

Oxytocin is a neuropeptide hormone, composed of nine amino acids and a ring formed by a disulfide bond between two cysteine residues (12). Oxytocin regulates social bonding, trust, empathy, childbirth, lactation, and stress responses. It modulates social behavior and emotional regulation (13). It is synthesized in the hypothalamus and released from the posterior pituitary gland into both the bloodstream and the brain(14). Chronic methamphetamine addiction disrupts oxytocinergic signaling, potentially impairing social cognition and stress regulation. Oxytocin interacts with dopamine and other neurotransmitters in reward circuits, and its deficiency may worsen addiction cycles by reducing social reward and increasing stress vulnerability(15)(16). In depression, oxytocin dysregulation is linked to impaired HPA axis function and increased cortisol release, exacerbating stress and depressive symptoms. Reduced oxytocin may also impair serotonin receptor expression, diminishing natural antidepressant effects and social connectedness(16).

Beta-endorphin is a peptide neurotransmitter, part of the endogenous opioid family, consisting of 31 amino acids (17). It is synthesized in the anterior pituitary gland from the precursor pro-opiomelanocortin (POMC), and related to the hypothalamic-pituitary-adrenal (HPA) axis. The HPA is first stimulated then induces production of corticotropic releasing hormone (CRH). This results in the simultaneous release of Adrenocorticotropic hormone (ACTH) and β-endorphins (18). Beta-endorphin provides potent analgesia, mood elevation, and stress relief. In the central nervous system, beta-endorphin bind mu-opioid receptors and exert their primary action at presynaptic nerve terminals. It exert analgesic effect and euphoria by inhibiting the release of GABA, an inhibitory neurotransmitter, resulting in excess production of dopamine. Dopamine is associated with pleasure (19). Methamphetamine addiction may dysregulate endogenous opioid systems, including beta-endorphin, reducing natural reward and pain inhibition. This leads to increased drug-seeking to compensate for blunted euphoria and heightened stress sensitivity (20). In depression, low beta-endorphin levels are associated with reduced mood, increased pain perception, and diminished stress resilience. Physical exercise, which boosts beta-endorphin, is recommended to improve mood in depression and support recovery in addiction (21). Chronic methamphetamine addiction and long-term depression both induce neurochemical disturbances through overlapping and reinforcing mechanisms. Chronic stress and neuroinflammation, common to both addiction and depression, activate the hypothalamic–pituitary–adrenal (HPA) axis, increasing glucocorticoid (cortisol) production, which is neurotoxic-particularly to hippocampal and prefrontal neurons-worsening cognitive and emotional symptoms (22). Pro-inflammatory cytokines such as IL-6 and TNF-α are upregulated, contributing to neurodegeneration and synaptic dysfunction. Oxytocin signaling is disrupted, reducing social reward, empathy, and stress resistance, while beta-endorphin synthesis and release are diminished, lowering pain tolerance and natural euphoria. Impaired neurogenesis and synaptic plasticity in the hippocampus and cortex further reduce cognitive flexibility and mood regulation (23). The loss of natural reward sensitivity perpetuates drug-seeking and deepens depressive symptoms. Ultimately, the interplay of these mechanisms creates neurochemical imbalance, reinforcing both chronic addiction and long-term depression, and complicating recovery efforts (24). The aim of this study is to assess serum oxytocin levels in patients with methamphetamine addiction and depression patients compared to healthy controls, and to evaluate their potential roles in mood regulation and reward behaviors.

MATERIAL AND METHOD

This study was an analytical observational research conducted by the College of Medicine at the University of Baghdad, from January to October 2024. In this study group 1: Twenty five persons with methamphetamine use disorder with duration periods of abuse was more than 6 months, and group 2: Twenty five patients with more than one year depression. Group 3: Thirty individuals as a healthy control were selected. The individuals of all groups were included in the study with matching sex, and age range between 18 to 60 years. The diagnosis of methamphetamine addiction and depression disorder were made by a specialist psychiatrist according to diagnostic criteria in Ibn-Rushed Psychiatric Teaching Hospital. Serum oxytocin and beta-endorphin were measured using the Enzyme-linked Immunosorbent assay (ELIZA). Blood samples were collected, and serum

was separated using a centrifuge. The isolated serum was then stored at -20°C for six months prior to analysis, with all samples analyzed simultaneously. Research permission was obtained with ethical approval from the Health Research Ethics Committee of the College of Medicine, University of Baghdad. And consent from the hospital and participants. Exclusion criteria were hepatic, renal, or cardiac disease, alcohol dependence, and comorbid substance use disorders.

STATISTICAL ANALYSIS

Data analysis was performed with SPSS software version 16.0. Continuous data are presented as mean ± standard deviation (SD), while categorical variables are reported as frequencies and percentages. For baseline comparisons, one-way ANOVA was used for continuous variables, depending on data distribution. The alpha level for statistical significance was established at a threshold of $p < 0.05$.

RESULTS

Demographic Characteristics:

The study included three groups: Addiction (No. =25), Depression (No. =25), and Control (No.=30) participants. The majority of participants were male across all groups, as shown in Table 1.

Table (1): Demographic Characteristics of Study Participants:

Characteristic	Addiction Group	Depression Group	Control Group
Sample size	25	25	30
Gender (M/F)	25/0	21/4	22/8

Age Distribution:

There is a match in the age groups and confirmed this have no significant differences in age distribution across groups P-value= 0.5099.

Table (2): Age Distribution across Groups.

Variable	Control (n=30)	Addict (n=25)	Depression (n=25)	p-value	LSD	Group Differences
Age years	32.57±10.77	33.56±10.91	36.00±10.52	0.5099	5.95	**No significant differences**

Baseline Comparisons:

In **table 3** the statistical analysis reveals significant differences across both biochemical markers. The control group consistently demonstrated higher levels of all measured substances compared to both the addict and depression groups. The addict group typically showed the lowest concentrations, while the depression group exhibited intermediate levels.

Table (3) Comparison of measurements across addicts, depression and control groups:

Serum parameters	Control (n=30)	Addict (n=25)	Depression (n=25)	p-value
Oxytocin (pg/mL)	40.80±11.40	20.70±3.16	23.19±3.08	<0.001*
Beta-endorphin (ng/L)	34.89±5.83	11.99±3.79	23.73±4.99	<0.001*

Note: Values presented as Mean ± SD. *Significant Value P<0.05

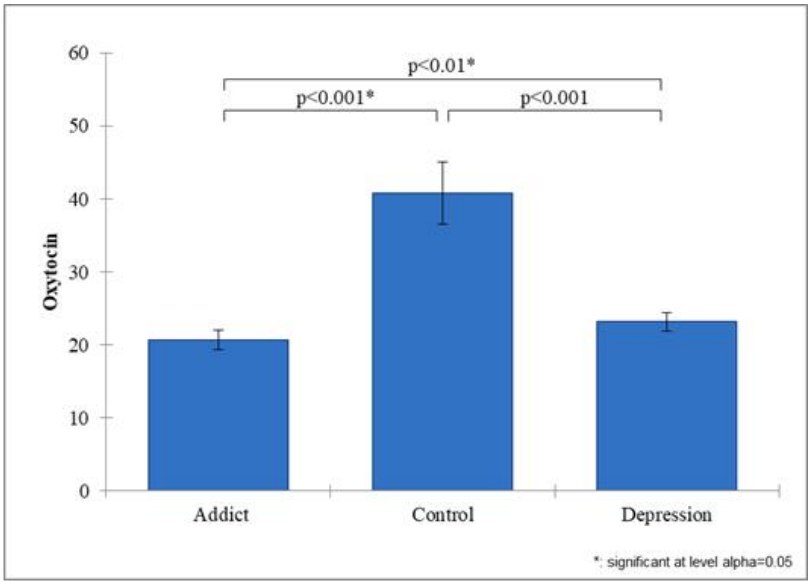

Figure 1: Comparison of mean oxytocin across groups.

In figure 1 oxytocin concentrations show the significantly lowest level in the addiction group with mean ± SD (20.70±3.16) *p*-value (<0.001), and the highest in controls with mean ±SD (40.80±11.40) *p*-value (<0.001), while the depression group exhibited intermediate level with mean ±SD (23.19±3.08) *p*-value (<0.001).

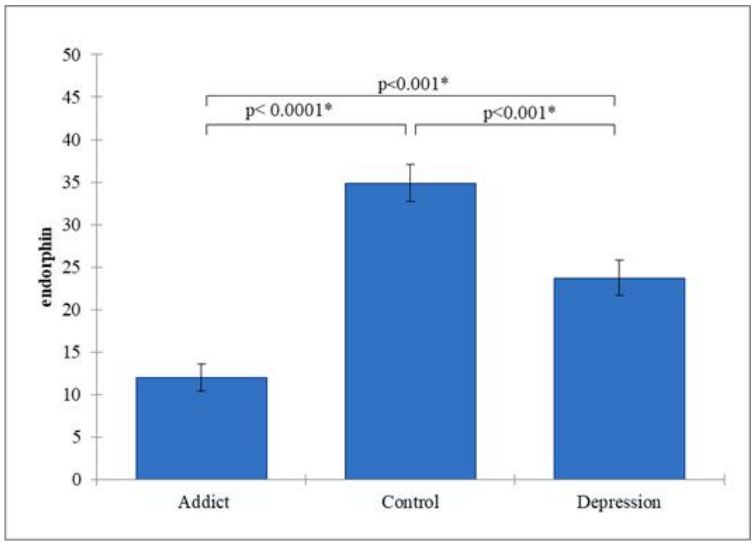

Figure 2: Comparison of mean beta-endorphin across groups.

In figure 2 Beta-endorphin concentrations show the significantly lowest level in the addiction group with mean ± SD (11.99±3.79) *p*-value (<0.001) and the highest in controls with mean ±SD (34.89±5.83) *p*-value (<0.001), while the depression group exhibited intermediate level with mean ±SD (23.73±4.99) *p*-value (<0.001).

Correlations and Associations:

Addict and depression groups showed positive correlations between oxytocin and beta-endorphin but no correlation between them in control group:

Addict group: r = 0.660, p < 0.001.

Depression group: r = 0.873, p < 0.001.

Depression group: r = 0.461, p < 0.01.

Oxytocin-Beta endorphin correlation was strongest in the depression group.

Table 4: Correlation for addict group (n = 25).

Variable	Oxytocin	Endorphin
Oxytocin	1.000	0.660***
	-	(p < 0.001)

Note: *** p < 0.001, ** p < 0.01, * p < 0.05

Table 5: Correlation for depression group (n = 25).

Variable	Oxytocin	Endorphin
Oxytocin	1.000	0.873***
	-	(p < 0.001)

Note: *** p < 0.001, ** p < 0.01, * p < 0.05

Table 3-9: Correlation for control group variables (n = 30).

Variable	Oxytocin	Endorphin
Oxytocin	1.000	0.461**
	-	(p < 0.01)

Note: *** p < 0.001, ** p < 0.01, * p < 0.05

DISCUSSION

The study individuals was selected within a predefined age range to minimize age-related variability. Interestingly, despite the random distribution of participants across groups, there was no statistically significant difference in age between them. Previous research indicating that, age does not significantly influence the level of oxytocin investigated in this study (25).

Chronic methamphetamine addiction and depression are characterized by distinct neurochemical deficits, with addicts showing the lowest levels of oxytocin and beta-endorphin compared to controls. In contrast, depression patient's exhibit intermediate reductions as **Table 3** showed.

These differences arise from various biological mechanisms: addiction involves neurotoxicity from prolonged substance use, Methamphetamine induces oxidative stress in the brain, largely through the generation of reactive oxygen species (ROS), which impair cellular function and contribute to neurotoxicity. Whereas depression stems from systemic dysregulation of

neurotransmitter synthesis, breakdown, and signaling. Oxytocin levels were found to be lowest in individuals with addiction, intermediate in those with depression, and highest in healthy controls. Chronic methamphetamine addiction, can elevate cortisol and disrupt hypothalamic pituitary adrenal (HPA) axis function, leading to suppressed oxytocin release and increased social withdrawal and anxiety. Methamphetamine also impairs serotonergic and noradrenergic neurotransmission and induces neuroinflammation, further reducing oxytocin synthesis and emotional regulation, a study used oxytocin as a treatment for methamphetamine addiction in rats to reduce anxiety and social deficits, which agreed with result(26). In depression, reduced oxytocin levels are associated with greater symptom severity and are thought to result from impaired HPA axis regulation and diminished serotonergic activity, which together contribute to mood and anxiety disturbances(27).

The oxytocin receptors throughout the CNS can be partially attributed to their action on dopaminergic reward pathways through activation of a variety of glutamate and dopamine receptors. Also, oxytocin in the brain can facilitate serotonin release and reduce anxiety-related behavior via oxytocin receptors. This effect is associated with the activation of serotonin receptors (28).

The study demonstrates significantly reduced β-endorphin levels in addiction and depression, with the lowest concentrations observed in addiction groups. Methamphetamine induced oxidative stress driven by dopamine auto-oxidation and reactive oxygen species (ROS) generation, damages dopaminergic and β-endorphin-producing neurons, exacerbating neuroinflammation and neurodegeneration (29). Study investigated the role of treatment beta-endorphin in mice addicts of cocaine who have low levels of beta-endorphin. The findings highlight that beta-endorphin mediates cocaine reward and relapse behaviours, potentially informing targeted addiction treatments (30). In depression, chronic stress dysregulates the hypothalamic-pituitary-adrenal (HPA) axis, leading to cortisol overproduction and diminished μ-opioid signaling, which further depletes β-endorphin stores and disrupts dopamine and serotonin modulation (31).

These mechanisms underscore oxytocin's importance as a neurobiological link between social behavior, stress response, and reward system, suggesting that therapies targeting oxytocin and beta-endorphin pathways may benefit individual affected by addiction and depression worldwide.

CONCLUSION

The results of the research highlight the significant decrease of oxytocin and beta endorphin that are associated with methamphetamine addiction and depression compared with controls. The observed decreases in both neurochemicals in the addiction and depression groups are consistent with previous research, emphasizing their deleterious impact on mood regulation and the reward system. Moreover, the significant association between these two measurements implies that changes in one system could exacerbate mood dysregulation and compulsive behaviors by causing disruptions in the other. These findings support the necessity of therapeutic approaches that target the oxytocin and beta endorphin systems in order to restore equilibrium in these neurochemical pathways and, eventually, enhance the effectiveness of therapy for methamphetamine addicts and depression patients.

REFERENCE

1. Cajanding RJM. MDMA-associated liver toxicity: Pathophysiology, management, and current state of knowledge. AACN Adv Crit Care. 2019; 30(3):232–48.
2. Al-Imam A, Michalak M. Iraq's Meth Crisis: Prioritizing Research to Combat Suicidal Ideation. Al-Kindy Coll Med J. 2024; 20(1): 78–9.
3. Jang WJ, Lee S, Jeong CH. Uncovering transcriptomic biomarkers for enhanced diagnosis of methamphetamine use disorder: a comprehensive review. Front Psychiatry. 2023;14(January):1–16.
4. Moszczynska A. Current and Emerging Treatments for Methamphetamine Use Disorder. Curr Neuropharmacol. 2021; 19(12): 2077–91.
5. Karrouri R, Hammani Z, Otheman Y, Benjelloun R. Major depressive disorder: Validated treatments and future challenges. World J Clin Cases. 2021;9(31):9350–67.
6. Yang X. Severe Depression : Etiology , Recovery , and Prevention. 2024; 6221:427–46.
7. Cui L, Li S, Wang S, Wu X, Liu Y, Yu W, et al. Major depressive disorder: hypothesis, mechanism, prevention and treatment. Vol. 9, Signal Transduction and Targeted Therapy. Springer US; 2024.
8. Moszczynska A. Neurobiology and clinical manifestations of methamphetamine neurotoxicity. Psychiatr Times. 2016; 33(9): 16–8.
9. Bertollo AG, Santos CF, Bagatini MD, Ignácio ZM. Hypothalamus-pituitary-adrenal and gut-brain axes in biological interaction pathway of the depression. Front Neurosci. 2025;19.
10. Bailey J, Oliveri A, Levin E. NIH Public Access. Bone. 2013; 23(1): 1–7.
11. Paulus MP, Stewart JL. Methamphetamine Use Disorder: The Next Addiction Crisis. JAMA Psychiatry. 2020;77(9):959–66.
12. Moustafa GO, Shalaby AM. The importance of amino acid and peptide chemistry in the treatment of the major diseases: Neuropeptides. Egypt J Chem. 2021;64(8):4469–86.
13. Walter MH, Abele H, Plappert CF. The Role of Oxytocin and the Effect of Stress During Childbirth: Neurobiological Basics and Implications for Mother and Child. Front Endocrinol (Lausanne). 2021;12(October):1–10.
14. Aulinas A, Lawson EA. The Oxytocin System and Implications for Oxytocin Deficiency in Hypothalamic-Pituitary Disease. Endocr Rev [Internet]. 2025;(February):1–31.
15. Edinoff AN, Thompson E, Merriman CE, Alvarez MR, Alpaugh ES, Cornett EM, et al. Oxytocin, a Novel Treatment for Methamphetamine Use Disorder. Neurol Int. 2022;14(1):186–98.

16. Li C, Wang H, Wang M, Chen C, Bai F, Ban M, et al. Oxytocin Attenuates Methamphetamine-Induced Apoptosis via Oxytocin Receptor in Rat Hippocampal Neurons. Front Pharmacol. 2021; 12(August):1–12.
17. Pilozzi A, Carro C, Huang X. Roles of β-Endorphin in Stress, Behavior, Neuroinflammation, and Brain Energy Metabolism. Int J Mol Sci. 2020 Dec 30;22(1):338.
18. Roschina O V., Levchuk LA, Boiko AS, Michalitskaya E V., Epimakhova E V., Losenkov IS, et al. Beta-endorphin and oxytocin in patients with alcohol use disorder and comorbid depression. J Clin Med. 2021; 10(23).
19. Sprouse-Blum AS, Smith G, Sugai D, Parsa FD. Understanding endorphins and their importance in pain management. Hawaii Med J. 2010; 69(3):70–1.
20. Volkow ND, Michaelides M, Baler R. The neuroscience of drug reward and addiction. Physiol Rev. 2019; 99(4):2115–40.
21. Abdel-Bakky MS, Amin E, Faris TM, Abdellatif AAH. Mental depression: Relation to different disease status, newer treatments and its association with COVID-19 pandemic (Review). Mol Med Rep. 2021; 24(6):1–17.
22. Lei AA, Phang VWX, Lee YZ, Kow ASF, Tham CL, Ho YC, et al. Chronic Stress-Associated Depressive Disorders: The Impact of HPA Axis Dysregulation and Neuroinflammation on the Hippocampus—A Mini Review. Int J Mol Sci. 2025; 26(7):1–13.
23. Ferrer-Pérez C, Reguilón MD, Miñarro J, Rodríguez-Arias M. Oxytocin signaling as a target to block social defeat-induced increases in drug abuse reward. Int J Mol Sci. 2021;22(5):1–21.
24. Dresp-Langley B. From Reward to Anhedonia-Dopamine Function in the Global Mental Health Context. Biomedicines. 2023;11(9).
25. Chung H, Choe S. Amphetamine-type stimulants in drug testing. Mass Spectrom Lett. 2019;10(1):1–10.
26. Baracz SJ, Robinson KJ, Wright AL, Turner AJ, McGregor IS, Cornish JL, et al. Oxytocin as an adolescent treatment for methamphetamine addiction after early life stress in male and female rats. Neuropsychopharmacology. 2022;47(8):1561–73.
27. TUMAN TC, YILDIRIM O, TUFAN AE. Evaluation of serum oxytocin levels in patients with depression, generalized anxiety disorder, panic disorder, and social anxiety disorder: A case-control study. J Surg Med. 2021;5(7):1–1.
28. Wang P, Wang SC, Liu X, Jia S, Wang X, Li T, et al. Neural Functions of Hypothalamic Oxytocin and its Regulation. ASN Neuro. 2022;14.
29. Shrestha P, Katila N, Lee S, Seo JH, Jeong JH, Yook S. Methamphetamine induced neurotoxic diseases, molecular mechanism, and current treatment strategies. Biomed Pharmacother. 2022;154.
30. Singh PK, Lutfy K. The Role of Beta-Endorphin in Cocaine-Induced Conditioned Place Preference, Its Extinction, and Reinstatement in Male and Female Mice. Front Behav Neurosci. 2021; 15(December): 1–8.
31. Salerian AJ. Endorphin Agonists for Severe Depression. Pharm Pharmacol Int J. 2015;2(2).