Journal of Case Reports and Reviews in Medicine

SCIVOLVE

Research Article

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# The Fundamental Role of Oxytocin in The Treatment of Human Depression: Efficacy of Oxytocin in Depressant Patients Less Responsive to The Standard Anti-Depressive Therapies

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**Received:** January 29, 2025; **Accepted:** February 26, 2025; **Published:** March 07, 2025

**How to cite this article:** Lissoni P, Messina G, Ceppodomo D, Rovelli F, Monzon A, Di Fede G. The Fundamental Role of Oxytocin in The Treatment of Human Depression: Efficacy of Oxytocin in Depressant Patients Less Responsive to The Standard Anti-Depressive Therapies. *J Case Rep Rev Med*. 2025;1(1);1-4.

## Abstract

The recent advances in Psycho-neuroendocrinology have suggested that depression-related serotonin deficiency is the simple consequence of an enhanced activity of the indole-2,3-dioxygenase (IDO), which transforms tryptophan into kynurenine instead of serotonin. Moreover, kynurenine, in addition to its neurotoxic action, has been proven to play an immunosuppressive activity by activating the regulatory T lymphocytes (T reg). IDO expression is stimulated by IL-17, whose brain production has appeared to be under a regulatory control played by ACE-ACE2 brain system. An enhanced expression of ACE with respect to ACE2 allows an enhance production of angiotensin II (Ang II) instead of angiotensin 1-7 (Ang 1-7). Ang II stimulates IL-17 secretion from glial cells, and IL-17 promotes glial cell release of other inflammatory cytokines, including IL-1beta and IL-6, which finally may activate the pituitary-adrenal axis, with a following enhanced cortisol secretion. On the contrary, Ang 1-7 has appeared to inhibit both IDO expression and IL-17 secretion, with a consequent anti-neuroinflammatory activity. In addition, recent studies have suggested a concomitant depression-related deficiency of oxytocin, which has been proven to play a fundamental role in the regulation of the affective and social relationships. Finally, pineal and endocannabinoid deficiencies have been also observed in depression. On these bases, a preliminary study was performed with oxytocin, the pineal hormones melatonin (MLT) during the night and 5-methoxytryptamine (5-MTT) during the day, low-dose Ang 1-7, and the non-psychotic cannabinol agent, cannabidiol (CBD) in depressant patients less responsive to the standard serotonin therapy. The study included 30 consecutive patients with diagnosis of depression according to Hamilton's score (HS) (severe grade: 12; moderate grade: 10; low grade: 8), who were less responsive to the classical antidepressant therapy with selective serotonin re-uptake inhibitors (SSRIs). A relatively rapid improvement of mood was achieved within the first moth of therapy in 26/30 (85%), with a complete normalization of HS in 5/30 (20%) patients. No therapy-related toxicity occurred. On the contrary, most patients referred a relief of anxiety and an improvement in the quality of sleep. Moreover, the results were compared to those observed in a historical control group of 20 depressant patients less responsive to SSRIs, who received MAO inhibitors as a second-line therapy. A clear benefit with a decline in HS greater than 30% was achieved in only 5/20 (25%) patients. Then, the results were significantly lower with respect to those found in patients treated with the neuroendocrine regimen. This preliminary study would suggest the possibility to treat the human depression in a new manner other than the classical serotonin therapy, consisting of the exogenous correction of the main possible depression-related neuroendocrine deficiencies involving the pineal function, the cannabinoid system activity, oxytocin secretion, and ACE2-Ang 1-7 axis. Then, further studies by detecting MLT, oxytocin, Ang 1-7 and FAAH, will be required to establish which neuroendocrine deficiency may particularly occur in each single depressant patient.

**Keywords: Angiotensin 1-7, Cannabinoids, Depression, IDO, Melatonin, Oxytocin**

## Introduction

According to the recent advances in the area of Psycho-neuro-endocrine-immunology (PNEI),[1-3] the classical interpretation of depression as a primary consequence of an altered serotonin metabolism has not been confuted, but they have allowed a more complete knowledge of depression pathogenesis with respect to the simple serotonin deficiency on the bases of four essential discoveries, consisting of 1). The role of oxytocin in the modulation of the affective life and faith sensibility[4-6] and its possible therapeutic use in psychiatric disorders, namely depression itself[7]; 2). The role played by the indole-2,3-dioxygenase (IDO) in opposing serotonin production, with a following serotonin deficiency, by piloting tryptophan metabolism

into the pathway of kynurenines[8-9]; 3). The involvement of IL-17 as the first event, which induces a neuroinflammatory status, and which could explain depression-related immune-depressive status because of the immunosuppressive action of IL-17 itself[10]; 4). The altered equilibrium between ACE and ACE2 brain expression, with a diminished ACE2 activity with respect to that of ACE, and a following enhanced production of angiotensin II (Ang II) than angiotensin 1-7 (Ang 1-7),[11] which plays anti-inflammatory neuroprotective effects.[12] Not only, but these four major pathogenetic dynamics of depression are connected between them, since IDO activity may be stimulated by Ang II and inhibited by Ang 1-7,[13] whose activity could be counteracted by some commonly used palliative drugs, such as pre-gabalin.[14] Moreover, Ang II stimulates IL-17 production, which in contrast is inhibited by Ang 1-7.[15] In addition, MLT has been proven to stimulate ACE2 expression,[16] with a consequent enhanced Ang 1-7 production in various body areas, including brain. Sleep deprivation also predisposes to psychiatric diseases,[17] since sleep disturbances may allow an abnormal accumulation of a neurotoxic protein, the alpha-synuclein, which inhibits the synaptic plasticity. The main consequence of serotonin deficiency is the endocrine failure of the pineal gland with a consequent diminished production of melatonin (MLT), and other less known pineal indole hormones, since they originate from serotonin itself.[18] The endocannabinoid system activity would be also decreased in depressant patients,[19] and this evidence could contribute to explain anhedonia-related depression, because of the fundamental role of the cannabinoid system in the perception of pleasure, as well as in the spiritual sensitivity.[20] Finally, as far as oxytocin is concerned (5-8), amygdala and thalamus represent the brain areas more expressing oxytocin receptors.[21] Moreover, it has been shown that a reduced thalamic oxytocin receptor expression is associated with a reduced social cooperation, a low sense of responsibility, as well as that low amygdala expression of oxytocin receptors may reduce defense mechanisms against stress and affective traumatic experiences (5-8). Some preliminary clinical studies have also demonstrated an oxytocin deficiency in depressant patients.[21] Previous preliminary clinical studies have suggested a potential efficacy of pineal hormone MLT alone[22] or in association with Ang 1-7,[23] as well as with the nonpsychotic-cannabinoid agents, such as cannabidiol (CBD),[18,24] in depressant patients, including those who did not respond to the conventional serotonin metabolism-related therapies. On these bases, a phase-2 study was planned to evaluated the clinical efficacy of a neuroendocrine regimen consisting of oxytocin in association with low-dose MLT, the other pineal hormone 5-methoxytryptamine (5-MTT), mainly produced during the light period of the day,[25] low-dose Ang 1-7, and mild-dose CBD as a nonpsychotic-cannabinoid agent,[18,24-25] in depressant patients less responsive to the standard antidepressant treatments.

## Patients and Methods

The clinical study included 30 consecutive depressant patients (M/F 11/19; median age: 64 years, range 21-95 years), who were followed at Biological Medicine Institute, or at the International Institute of PNEI in Milan, for their depressive disease. Eligibility criteria were, as follows: diagnosis of depression evaluated according to Hamilton test (HS),[26] lack or less response to the conventional commonly employed antidepressant serotonin-founded treatment with selective serotonin re-uptake inhibitors (SSRIs), or personal refusal because of important subjective negative effects. After the approval of the Ethical Committee, the clinical protocol was explained to each patient and their relatives, and a written consent was obtained. According to HS, the diagnosis of depression required values greater than 7, with a low grade of depression with values between 8 and 17, moderate grade of depression between 18 and 24, and severe depression for values greater than 24. A severe depression was present in 12/30 (40%) patients. Depression was moderate in other 10/30 (33%) patients, and low in the remaining 8/30 (27%) patients. All drugs were given orally. Moreover, oxytocin, was administered in gastro-protected capsules to counteract gastric destruction of the peptide. Oxytocin wad given at 2 mg twice/day. According to their circadian secretion, MLT and 5-MTT were given respectively at 20 mg during the dark period of the day, generally 30 minutes prior to sleep, and at 10 mg during the light phase of the day, generally in the first afternoon. Finally, CBD and Ang 1-7 were given twice/day, respectively at 20 mg and at 0.5 mg. The low-dose of Ang 1-7 was justified by the demonstrated stimulatory action of the pineal MLT on ACE2 expression, with a following enhanced endogenous production of Ang 1-7 itself.[17] The treatment was continued without interruption for a minimal period of 2 months, by maintaining at least for the first weeks of therapy the same SSRI treatments, and by slowly reducing their doses until the complete interruption. Moreover, to prepare the consciousness of patients to the psychological changes induced by the treatment, we started with the administration of the only MLT for some days to replace the biological circadian rhythms and to improve the quality of sleep, followed by the administration of Ang 1-7 and CBD to improve both the sense of force and to reduce the intensity of anxiety, and finally as a last treatment the administration of oxytocin in an attempt to improve the affective life of patients, the sexual interest, and the social and inter-personal relationships. HS was made before the onset of therapy and at monthly intervals for the first 3 months of therapy. Data were reported as mean +/- SE, and statistically evaluated according to the chi-square test, the Student's t test, and the analysis of variance, as appropriate.

## Results

A rapid improvement in mood and anxiety in association with an evident subjective enhancement of the sense of force was referred by most patients within the first days of therapy, while a clear improvement in the affective life and social relationships was observed only after the beginning of oxytocin administration. A normalization of HS was achieved after at least one month of therapy in 9/30 (30%) patients. In addition, 5 of these patients (56%) referred a sense of renaissance, and a well-being associated with a serenity status never experienced in their past life. Moreover, a decline in HS greater than 30% was observed in other 15/21 (71%) patients. Therefore, a decline in HS greater than 30% was obtained in 24/30 (80%) patients. As far as the efficacy of therapy in relation to the degree of depression, as shown in Table 1, a decline greater than 30% in HS was achieved in 9/12 (75%) patients with severe grade of depression, with a complete normalization of its score in 4/12 (33%) patients. The same benefit in terms of decline greater than 30% in the HS was achieved in 8/10 (80%) patients with moderate grade of depression, and in 7/8 (88%) patients with low depression grade. These differences were not statistically significant. After the two months of the programmed therapy, 28/30 (93%) patients decided to continue the treatment because of its evident benefits for their affective and social life, whereas the other 7/30 (23%) patients decided to interrupt the programmed antidepressant therapy, which in any case was really better tolerated. No biological toxicity was observed on study. Moreover, no particular negative subjective effect was referred, with the only transient and apparent increase in the anxiety for only few days of MLT administration, probably due to the increased emotional reactivity promoted by MLT itself. In addition, the results of the study were compared to those obtained in a historical control group of 20 sex-, age-, and clinical symptomatology-

matched depressant patients less responsive to the standard therapy with SSRIs, who received MAO inhibitors as a second-line therapy for their disease. A decline in HS greater than 30% was observed in only 5/20(25%) patients, then the results were significantly lower than those achieved in patients, who received the neuroendocrine regimen proposed in the present preliminary study (5/20 (25%) vs 24/30 (80%), P<0.01).

## Discussion

The present study, which was performed in a considerable number of patients, would demonstrate the efficacy of a new strategy in the treatment of human depression, consisting of the exogenous correction of the main depression-related neuroendocrine deficiencies other than that of serotonin, including the diminished endogenous production of the pineal hormone MLT, Ang- 1-7, oxytocin, and cannabinoids. This neuroendocrine regimen has appeared to be effective in the relief of the main depressant symptoms, represented by sleep disturbances, decline in mood, asthenia, and difficulty in the social relationships. In particular, the results of this study would suggest the fundamental role of oxytocin in the treatment of human depression, because of its capacity to improve the affective sensitivity, then the social relationship, and consequently the mood of patients. Then, the most evident difference played by this neuroendocrine approach to the treatment of depression with MLT, cannabinoids, Ang 1-7, and oxytocin with respect to the standard antidepressant therapies would consist of the more evident improvement in the affective life and spiritual sensitivity, probably mainly induced by oxytocin, the so-termed hormone of Love and Faith.[21] Finally, Ang 1-7 could represent the most active agent to improve depression-related asthenia, and enhance the sense of force, then the personal self-esteem. In addition, it is also interesting to remark that the neuroendocrine regimen may be effective either alone, or in association with the commonly employed antidepressant drugs, to improve their efficacy, and to reduce their subjective and objective negative effects, because of the neuro-protective and cardio-protective activity of both MLT and Ang 1-7. However, further randomized studies by comparing these results with respect to those obtained by the common antidepressant strategies will be required to confirm the efficacy of the neuroendocrine regimen proposed by the present study. Finally, further clinical studies by evaluating the pineal function through the investigation of MLT light/dark rhythm, serum levels of both Ang 1-7 and oxytocin, will be required to establish whether the efficacy of the neuroendocrine regimen proposed in the present study may be more active in the presence of some endogenous neuroendocrine deficiencies, particularly that of oxytocin, or whether the treatment may be also relatively independent with respect to the neuroendocrine endogenous conditions of patients. Gaba-A[27] and endocannabinoid[28] deficiencies have been also described in depressant patients, which could explain the occurrence of anxiety and loss of pleasure perception, respectively. In conclusion, depression physiopathology would have to be reinterpreted as the consequence of a multiple possible neuroendocrine and neurotransmission alterations, involving serotonin, oxytocin, Gaba-A, endocannabinoid, and Ang 1-7 deficiencies in association with an enhanced production of the neurotoxic molecule, kynurenine. Then, each depressant patient would have to be investigated to identify the main neuroendocrine deficiency occurring in his disease.

**Table 1.** Clinical results according to Hamilton's score in 30 depressant patients treated with an oral neuroendocrine regimen with oxytocin, melatonin, cannabidiol, and angiotensin 1-7 in relation to the degree of depression, by considering the treatment as effective in the presence of a decline in Hamilton's score greater than 30%.

| PATIENTS | n | CLINICAL EFFICACY |
|---|---|---|
| OVERALL PATIENTS | 30 | 24/30 (80%) |
| -SEVERE GRADE | 12 | 9/12 (72%) |
| -MODERATE GRADE | 10 | 8/10 (80%) |
| -LOW GRADE | 8 | 7/8 (88%) |

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