UNIVERSITATEA DE MEDICINĂ ȘI FARMACIE
GRIGORE T. POPA IAȘI

# PHD THESIS RESUME

# The relevance of oxytocin in psychiatric affective disorders - bio-psycho-social implications

**PhD Student**

**DR. PĂDURARIU MANUELA**

**Scientific leader**

**Prof Dr Ștefănescu Cristinel**

SUMMARY

# I. The state of knowledge

## Chapter I.3. Complex connections between oxytocin and the neurotransmitter system in affective disorders

The notion that oxytocin is a mediator for other neurotransmitter systems and that its key role could be integrating the effects of other molecules has been speculated by many researchers who have investigated the complex link between the oxytocinergic system and various neurotransmitters in several experiments. The role of the neuromodulatory peptide is speculated and empirical by the differentiated effects of oxytocin, both social, emotional and behavioral, which differ greatly depending on the context of the experimental situation, but also on the various factors which may be present (25-31).

These stimuli have some relevance in activating the oxytocin system when they are labeled by the subject as having a certain significance relevant to the subject. Thus, stimuli that can be interpreted by the subject as potentially dangerous, such as the presence of a foreign person or with traits that suggest mistrust, or a hostile environment will trigger a completely different oxytocin-mediated reaction compared to the presence of either a very person. close or positive, encouraging facial expressions that indicate a friendly environment, while preserving the other environmental conditions.

The fact that oxytocin can cause different reactions precisely depending on how the environment is perceived by the subject, is based on the hypothesis that oxytocin plays its role indirectly, orchestrating the activity of several neurotransmitter systems.

In fact, the way in which oxtocin plays its roles may be much more direct than originally thought. Thus, compared to other hormones, oxytocin is the most direct marker of central events, being secreted into the neurohypophyseal circulation from the nerve endings of the hypothalamus.

Compared to the action of oxytocin, hormones such as ACTH or prolactin have secretion dependent on stimulatory or inhibitory factors that act at the hypothalamic level to activate / inhibit their secretion, and in practice their action could only be signal amplification by activating G-protein coupled receptors. initiate further activation of specific hormones. As with corticosterone, this is an even greater amplification, as ACTH released from the pituitary continues to stimulate specific ACTH receptors in the adrenal glands, activating corticosterone secretion (43).

Thus, these mechanistic aspects could explain the theoretical aspects described in chapters I.4. (Oxytocin and psycho-social roles), I.5. (Relevance of oxytocin in psychiatric disorders) and I.6. (Oxytocin and psycho-somatic manifestations in affective disorders).

# II. The original part

The justification for choosing the subject of study resides from the current state of knowledge, incomplete and nonlinear data on the central roles of the oxytocin system, but at the same time also from the need for a more intimate understanding of the biological mechanisms underlying the psychic processes in neuro-psychiatric disorders.

The starting point for understanding the connection between oxytocin and psychiatric disorders is post-partum depression, which has been the basis of many studies on the

relevance of oxytocin in psychiatric disorders, and has opened a research direction that could have special implications in complementing the knowledge from biological processes. mental illness. With each important discovery on the ways of functioning of the central biological systems it opens and it was different therapies, alternative or complementary to the standard therapies in various neuro-psychic disorders.

Our scientific approach is justified in the present context of scientific knowledge regarding mental disorders and especially affective disorders. With all the efforts made so far to identify the pathophysiology, some valid clinical biomarkers for a diagnosis of certainty, but also for a better understanding of the intimate mechanisms associated with the mental disorders and their specific treatment, so far we do not have sufficient conclusive data , and the diagnostic process is still based on subjective clinical criteria, as well as with the therapeutic approach.

Thus, mental disorders are understood rather in terms of dimensional and categorical type and thus diagnosed with an increased degree of subjectivity and treated according to the clinical picture without being able to use objective biological markers, as is the case with other medical specialties.

Several elements specific to this system determine that interpretations of these results are difficult and subject to errors. Among these elements are the reduced half-life of oxytocin, the central and peripheral distribution of oxytocin receptors, the major influence of the environment in which the research is conducted, the sex of individuals but probably many other factors that we are not aware of at the moment. their.

The current data do not allow us to draw definitive and clear conclusions on this aspect, but we can speculate a major and categorical influence of oxytocin in a multitude of behavioral patterns as well as psycho-emotional patterns that are the basis of many mental disorders but at the same time. , we also speculate on the existence of complex links between oxytocin and the other neurotransmitters.

In this context, we decided to analyze the oxytocin system, but also its relation with cortisol in depression, considering that on the one hand increased cortisol is associated with depression, and on the other hand oxytocin would be a modulation factor at that time. when cortisol is released in excess.

The irritable colon has many links with depression, including common etiology and stress, therapeutic response to antidepressants, increased frequency of association of the two pathologies in the clinic, but also the presence of oxytocin and serotonin receptors in the digestive tract. Also, cortisol appears to be of major relevance in both depression and colon irritation, both of which are correlated with both etiopathogenic and biological stress. In this context, in this paper we analyzed this relationship between oxytocin and cortisol in depression but also in depression accompanied by irritable colon, analyzing the peripheral concentrations of these molecules in two different groups of patients, with depression and with depression and irritable colon and we compared and analyzed also according to a number of factors that relate to the patient's particularities but also to the depression they suffered.

The objectives of the present paper concern the relevance of oxytocin in affective disorders from several angles. First, we tried to identify if peripheral neurohormone oxytocin concentration changes in patients with major depression and how the oxytocin level changes and whether it is influenced by other parameters such as age, sex, or intensity of symptoms or suicidal ideation.

At the same time, we studied whether in the depression associated with irritable colon, oxytocin could play a role, given the pattern of peripheral distribution of oxtocin receptors, but also the importance of the brain-digestive system in psychiatric disorders. At the same time, it is relevant for this idea that in clinical practice we encounter somatoform type symptoms very often associated with a psychiatric disorder, and digestive symptoms are the most frequently reported by patients.

Also, considering the numerous evidence of the interaction of oxytocin with the HPA axis, we sought to analyze this connection between the two systems by analyzing peripheral concentrations of oxytocin and cortisol in patients with major major depression, but also in patients with major depression and irritable colon.

The questions we are trying to solve by this scientific approach concern firstly the notion that oxytocin might be involved in the mechanisms of depression and at the same time we could verify this assumption by measuring the level of oxytocin in these patients. Secondly, it is well known that in affective disorders, the connection between the central and peripheral nervous systems is strong and, rarely, the somatic symptomatology in depression or anxiety exceeds in intensity the psychic one.

Thus, another hypothesis of the present study is of particular interest to this connection between the brain and the rest of the body, speculating that oxyokine may be a mediator of these somatic manifestations in mental disorders, such as depression. The basis of these speculations is the wide distribution of oxytocin receptors, somewhat symmetrical with the distribution of the vegetative nervous system. At the same time, the peripheral roles of oxytocin are beginning to be studied, but they are still far from being fully understood.

### II.2.1 The first study

In the first study, we wanted to analyze the level of peripheral oxytocin in a group of 15 patients diagnosed with major depression (severe depressive episode or recurrent depressive disorder with current severe episode) and to investigate whether the oxytocin level correlates with the intensity of depressive symptomatology.

To carry out this study we used the Hamilton psychometric scales for depression and Hamilton for anxiety, we obtained socio-demographic data on patients and dosed the oxytocin level. The results were statistically analyzed, reported and discussed.

Study hypotheses:

1. The level of oxytocin is correlated with the intensity of depression.

2. The level of oxytocin is correlated with the intensity of the anxiety symptoms.

3. The level of oxytocin in depression is influenced by parameters such as sex or age.

4. Oxytocin level is altered in depression with suicidal ideation compared to depression without suicidal ideation.

### II.2.2. The second study

For the second study we wanted to investigate the relationship between oxytocin and cortisol in depression and depression, respectively, with irritable colon. To carry out this research we selected a total number of 30 patients with major depression. Of the total of 30

patients, a number of 15 patients had major depression and irritable colon, and 15 patients had only major depression without irritable colon.

The hypotheses of the second study are the following:

• Oxytocin may be involved in the relationship between depression and irritable colon

• Oxytocin may modulate cortisol levels in depression

• Oxytocin may influence cortisol levels in depression accompanied by irritable colon.

II.2.3. Third study (study on experimental animals)

This study was conceived on the grounds that the other studies in human subjects regarding the administration of oxytocin are difficult and relatively restrictive, and on the other hand due to the difficulties of controlling the environmental factors, which as we know they can the major influence is the interpretation of the results regarding oxytocin. At the same time, testing only by correlative methods of oxytocin levels in depression does not definitively demonstrate the causal relationship between oxytocin and depression, but also the potential therapeutic effect.

Thus, for these reasons we conducted this study using animal models of depression made with the help of forced swimming test. The study itself involved evaluating the antidepressant effects of intraperitoneal oxytocin by measuring conventional depression indicators that will be described below.

Study hypothesis

- Oxytocin determines the modification of behavioral indices of depression in the experimental animals (measured by the latency time for cleaning, the latency time for escape from stress situations and the time of social interaction).

## Chapter II.2. Materials and methods

### II.3.1. Studies on human subjects

The studies were performed on the patients who were recruited from the Socola Regional Psychiatry Institute. Patients were selected from patients who had the diagnosis of severe depression with or without anxiety and were either in the first episode or known with the diagnosis of recurrent depression (severe depressive episode or severe depressive disorder with current severe episode). Patients were selected based on the inclusion and exclusion criteria set out below, and patients signed informed consent prior to enrollment in the study.

The patients included in the study were selected on the basis of inclusion criteria which are shown below. Patients who presented the exclusion criteria set forth below the inclusion criteria were excluded from the study.

In order to carry out this study, the following inclusion criteria were used:

• - patients aged 18 to 65 years

• - patients diagnosed with major depression

• patients with a score greater than 26 points on the HAMD scale

• - patients admitted to the Socola Psychiatry Institute, Iasi

• - school-aged patients who could understand and sign informed consent.

The following exclusion criteria were used

• illiterate patients

• patients with dementia

• patients with mental retardation

• patients with organic affective disorders

• patients with psychotic disorders

• patients with endocrinological disorders

pregnant or postpartum patients

• the presence of some decompensated medical conditions

• patients with endocrinological disorders

• patients using cortisol-based drugs.

Clinical methods used

The clinical interview was used to establish the diagnosis of severe depression, which was necessary to establish the diagnosis of severe depression, but also to exclude other medical conditions that may interfere with the interpretation of the results of the study, as mentioned above, within the exclusion criteria. .

In order to establish the diagnosis of severe depression, both the clinical criteria for diagnosis of severe depression evaluated according to the ICD-10 criteria, but also meeting the DSM-IV criteria, were respected.

At the same time, the condition that the score for the Hamilton Depression Scale (HAMD) (143) was higher than 26 points was also respected.

The Rome criteria

The Rome criteria were developed by a group of international experts in the field of gastrointestinal functional disorders. The Rome IV criteria defined irritable bowel syndrome as a functional bowel disease in which recurrent abdominal pain is associated with defecation or alteration of bowel habits (141).

Chemical method for dosing of peripheral oxytocin level (144).

**II.4. Animal studies**

The experiments in the third study were performed on white, male, Wistar rats, weighing 200-250 g, at the time of beginning the experiment. Animals used were homogeneous in weight, age and sex.

The animals were kept in a room controlled by temperature and environment (22 ± 2 ° C, 12-hour cycle, 40-60% relative humidity). The animals were acclimated to the specific laboratory environment for 10 days prior to the start of the experiment.

The rats were fed a standard lab diet with rat pellets, according to the dietary requirements of McCollum. Except for the behavioral testing periods that require food limitation and two hours before oxytocin administration, the animals received food and water ad libitum.

The handling of rats complied with the current European and national regulations on scientific research using animals from the Law on Animal Experimentation and Animal Health and the Romanian Welfare Law and all procedures were in accordance with the Council of the European Communities.

• Forced swimming test;

• The open maze test;

• The splash test;

o Tricameral maze test;

o Radial arm-maze test maze test;

o The higher maze.

# Chapter II.3. Results

## II.3.1. Relevance of oxytocin in depression

### II.3.1.1. Socio-demographic data

To achieve the objectives of study 1, we selected a number of 15 patients diagnosed with major depression. Of these 15 patients studied, 9 patients were men, and 6 were women, with 60% being men compared to 40% women.

### II.3.1.4. Correlation between oxytocin and depression intensity

The level of peripheral oxytocin was evaluated in all patients in the present study. The first hypothesis of the study is that oxytocin could be correlated with the intensity of depression measured using the HAMD scale. Patients in the study group had an average oxytocin concentration of 285.39 ± 63.18 pg / ml.

Association between oxytocin level and HAMD depression scores

In the table below (table 14) are summarized the main aspects of the study groups analyzed regarding the HAMD scores and the oxytocin concentration values for the studied group.

Table II.14. Statistical data in the oxytocin-HAMD scores relationship

| Variable | N | N* | Mean | SE Mean | | StDev | Minimum | Q1 | Median | Q3 | Maximum |
|---|---|---|---|---|---|---|---|---|---|---|---|
| oxitocină | 15 | 0 | 285,4 | 13,1 | | 61,7 | 182,0 | 235,0 | 308,4 | 322,0 | 378,0 |
| HAMD | 15 | 11 | 30,091 | 0,547 | | 1,814 | 28,000 | 28,000 | 30,000 | 32,000 | 33,000 |

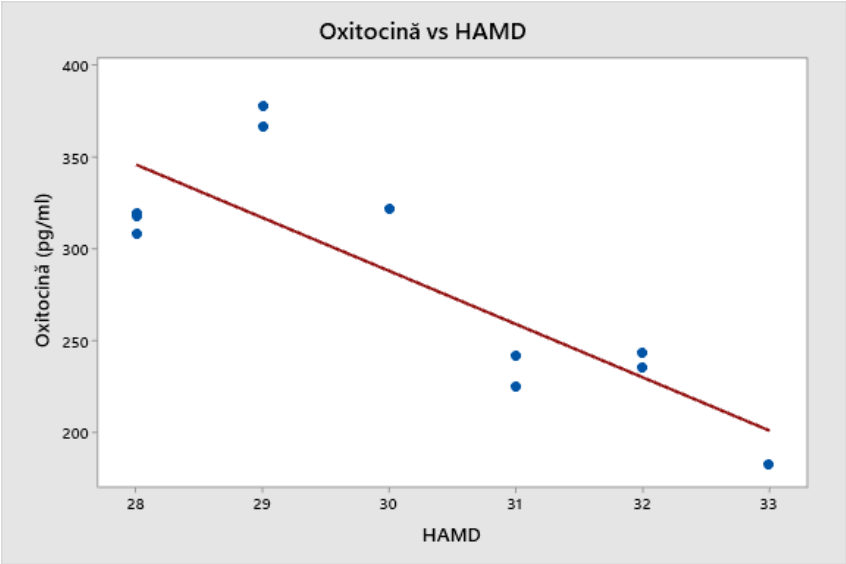


Figure II.21. Pearson correlations between oxytocin concentration and HAMD scores

Pearson correlations – pairs

| Sample1 | Sample 2 | Correlation | 95% CI for ρ | P-Value |
|---|---|---|---|---|
| HAMD | Oxiytocin | -0,832 | (-0,955; -0,464) | 0,001 |

We correlated the oxytocin levels measured in the peripheral blood with the scores obtained by the study patients on the Hamilton depression scale. The results clearly show an inversely proportional correlation between depression intensity and oxytocin concentration (r = -0.95; p = 0.001) (Figure 9). The correlation observed between the 2 parameters, oxytocin on the one hand and the HAMD depression score, on the other hand in patients with major depression is statistically significant (p <0.05).

### II.3.1.5. Correlation between oxytocin and anxiety intensity (2nd hypothesis of the study)

To test this hypothesis we correlated the levels of oxytocin measured in peripheral blood from patients with major depression with the scores obtained by the patients in the study on the Hamilton anxiety scale. The results obtained by analyzing the HAMA scale scores and oxytocin concentrations with the help of Pearson-type correlations revealed inverse proportional correlations between these 2 parameters with poor correlation power and no statistical significance (N = 15, r = -0.39, p = 0.6).

## II.3.2. Oxytocin-cortisol relationship in depression accompanied by irritable colon (2nd study)

### II.3.2.2. Oxytocin level analysis

Given the current knowledge about oxytocin and the dynamics of social and gender influences, we found it useful to evaluate the serum oxytocin concentration based on certain socio-demographic indices in order to observe the possible differences that may exist between

Oxytocin level in relation to various demographic parameters

Table II.20. Oxytocin level (pg / ml) by age group

| Age (years) | N | Oxytocin (pg/ml) | DS |
|---|---|---|---|
| 20-29 | 1 | 247,4 | |
| 30-39 | 2 | 228,75 | 30,15 |
| 40-49 | 5 | 261,32 | 33,3 |
| 50-59 | 6 | 231,58 | 17,80 |
| above 60 | 1 | 199,5 | |

### II.3.2.2. Analysis of oxytocin levels in depression associated with irritable colon

We tested hypothesis 1 of the study: oxytocin might be involved in the relationship between depression and irritable colon.

We compared the 2 groups of patients with irritable colon and without irritable colon in terms of plasma oxytocin level measured in pg / ml to see if there is a statistically significant difference between patients with irritable colon and patients without irritable colon in terms of of peripheral oxytocin level.

Descriptive statistics

| Sample | N | Media | DS | SE Media | 95% CI for μ |
|---|---|---|---|---|---|
| Irritable colon | 15 | 240,03 | 33,77 | 9,02 | (220,90; 259,89) |
| Without irritable colon | 15 | 285,4 | 63,2 | 19,1 | (242,9; 327,8) |

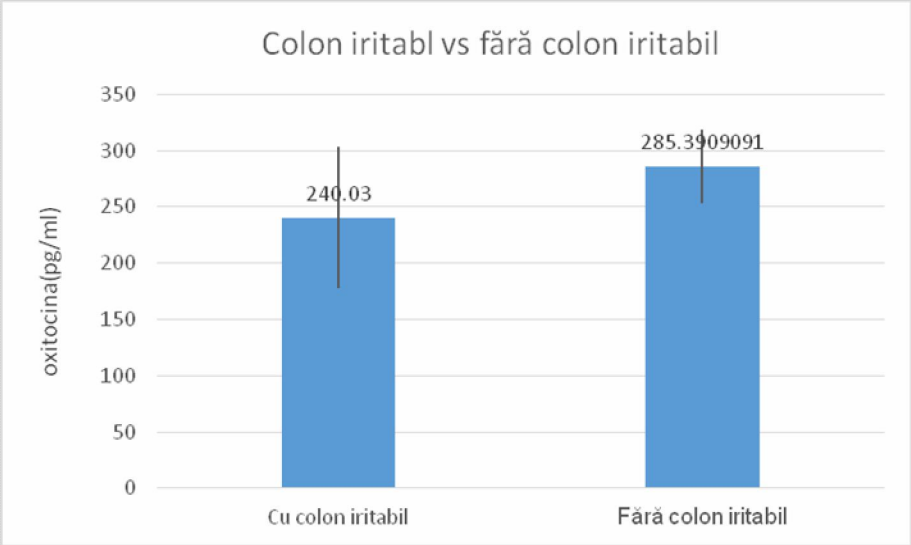


Figure II.33. Comparison of oxytocin level in patients with irritable colon vs patients without irritable colon (p = 0.024, <0.05)

We compared the oxytocin concentration for the two groups of patients in the study. The group with patients with depression and irritable colon showed a lower plasma oxytocin

level (M = 240.03 ± 63.18) than the patients who did not have irritable colon (M = 285.39 ± 32.56), and the results were statistically significant (p = 0.024, <0.05) (Figure 33).

• Pearson correlations between peripheral oxytocin levels and HAMD scores

Next we analyzed whether there is any association between depression intensity, evaluated in this case by the scores obtained on the Hamilton scale for depression and oxytocin concentration (pg / ml). To investigate this issue statistically, we used Pearson correlations and analyzed the factors r and p.

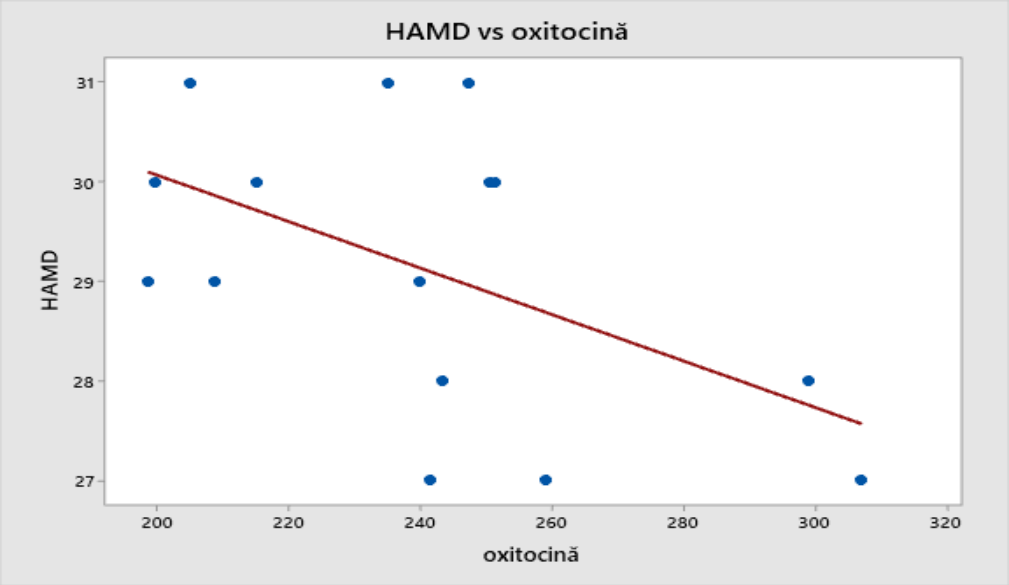


Figure II.34. Pearson correlations between HAMD scale scores and oxytocin levels

Pearson pair correlations

| Sample 1 | Sample 2 | Correlation | 95% CI for ρ | P-Value |
|---|---|---|---|---|
| oxytocin | HAMD | -0,521 | (-0,815; -0,011) | 0,047 |

The level of oxytocin measured for patients with major depression and irritable colon appears to be inversely correlated with the HAMD scale values in our study. Thus, the highest values of the HAMD score are associated with low values of the oxytocin concentration, whereas subjects who had a lower score on this scale had higher oxytocin concentrations (r = -0.52, p≤ 0.05) (Fig. 34).

Basically, while patients with higher depression intensity had lower plasma oxytocin values, patients with slightly lower depression intensity had higher plasma oxytocin levels. For these correlations, statistically analyzed using Pearson correlations, we observed statistical significance.

### II.3.2.5. Oxytocin-cortisol relationship in depression with irritable colon

Testing hypothesis 3: Oxytocin influences cortisol levels in depression accompanied by irritable colon

• Correlations between oxytocin and cortisol

To test this hypothesis, we first analyzed the direct correlations that might exist between oxytocin and cortisol in patients with depression and irritable colon in our study group. To analyze the correlations between these 2 parameters we used Pearson correlations, as can be seen in figure 42.

Pearson pair comparisons

| Sample 1 | Sample 2 | Correlation | 95% CI for ρ | P-Value |
|---|---|---|---|---|
| cortizol_2 | oxitocină_3 | 0,668 | (0,114; 0,905) | 0,025 |

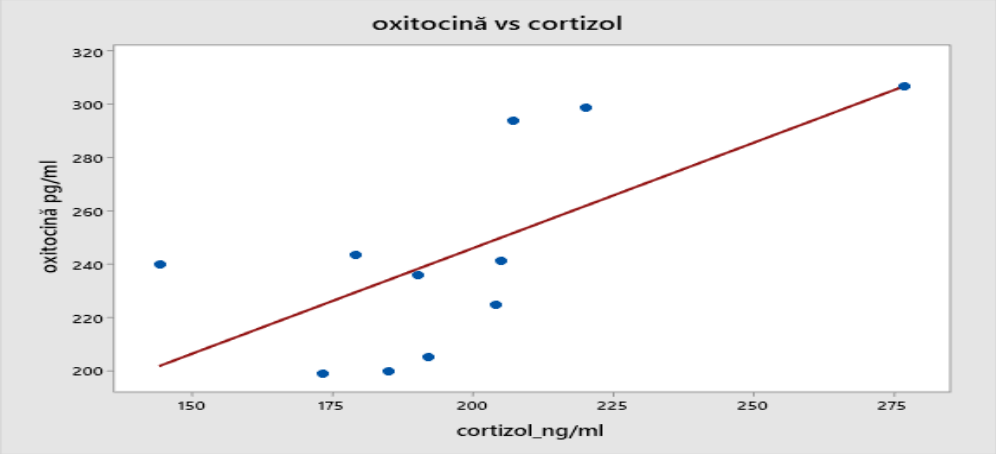


Figure II.42. Pearson correlations between oxytocin (pg / ml) and cortisol (ng / ml) concentrations (r = 0.66; p = 0.02) in patients with depression and irritable bowel

## II.3. Animal model study results (III study)

The experiment on animal models of depression was performed to test the therapeutic potential of oxytocin, taking into account the associated ethical implications if we chose the oxytocin administration variant on human subjects, but at the same time due to the possibilities of controlling the environmental factors that as we know, they can greatly influence the exitocin secretion and may interfere with the final results of the study, generating potential errors of interpretation. The study animals group were always compared with the control group and the analyzed results to see the statistical significance.

In this study, animal models of depression were used, made with the help of the forced swimming test, which, as we have mentioned in the chapter on Materials and methods, is based on the theory of learned helplessness. We chose for this study, the forced swimming test as a method of making these animal models, due to the ease of production but also to the choice of methods that are less harmful to animals.

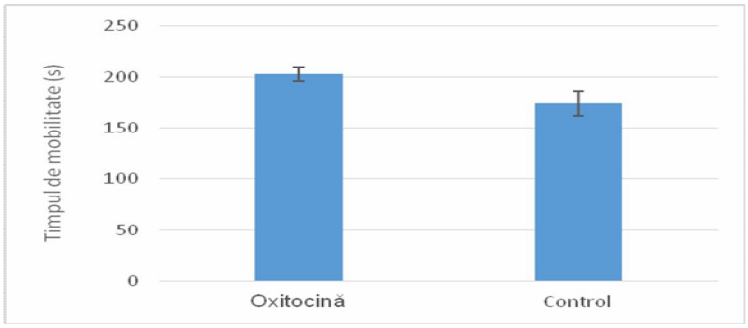


Figure II.48. Effects of oxytocin administration on mobility time (seconds) (p = 0.08)

### III.3.2. Splash test

We performed this test to see how care time changes in animal models of depression when they are dirty on their fur after oxytocin administration. In animal models of depression, the fur cleaning behavior represents one indicator relevant to depression. The results were compared with a control group that received only saline.

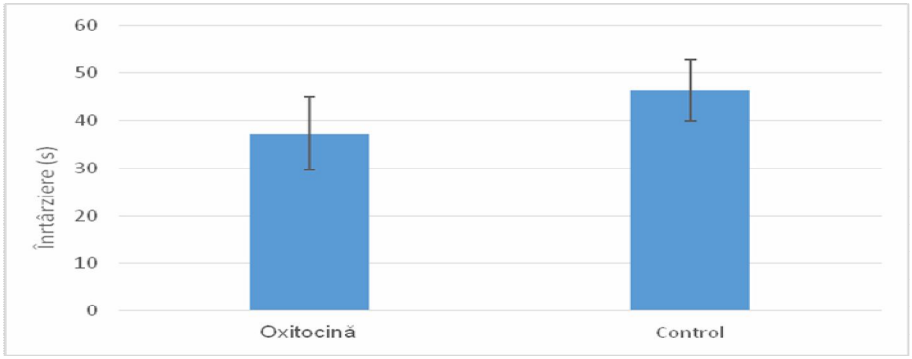


Figure II.50. Effects of intraperitoneal oxytocin administration on delayed care behavior. Values are expressed as mean ± D.S.

In this experiment, we observed that oxytocin-treated animals showed a shorter delay time to the first care behavior (37.3 ± 7.6 s), compared to the control group that had a time of 46.3 ± 6.4 s, as shown in Figure 50, under the same experimental conditions.

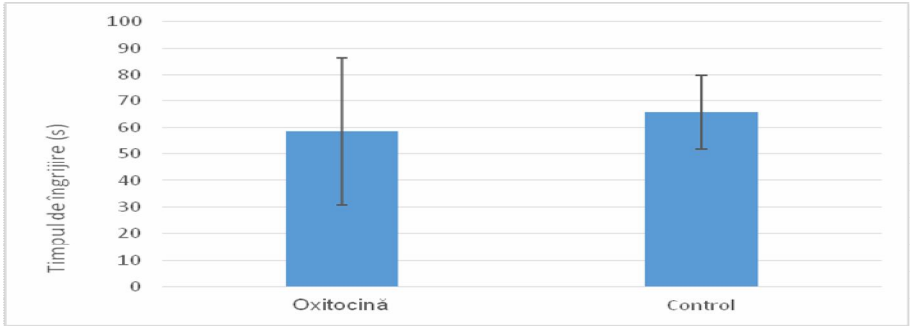


Figure II.50. Effects of intraperitoneal oxytocin administration on grooming behavior.

### III.3.3. Three-room sociability test

In this test, we analyzed several useful indicators for observing socializing behavior. Thus, we analyzed the time spent in the inhabited room (during the first testing phase), the preferences for the foreign animal (the contact time with the familiar animal versus the foreign animal) and anxiety behaviors when exposed to social stimuli (care and immobility).

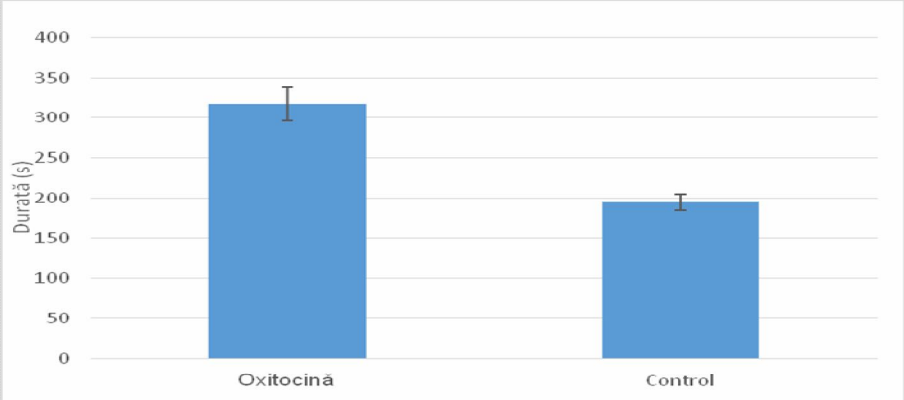


Figure II.51. Effects of oxytocin administration on the time spent in the inhabited room

## Chapter II.5. Conclusions

Following the statistical analyzes for the 3 studies carried out within the presented project we can draw the following conclusions:

- Oxytocin levels appear to increase with the intensity of depressive symptoms. Thus, patients with more pronounced depression had a lower level of oxytocin compared to patients who showed a lower intensity of depressive symptomatology, as measured by the Hamilton depression scale.

- Oxytocin concentration does not change with increasing anxiety symptoms in major depression.

- Age or sex did not have statistically significant influence on the level of oxytocin in major depression.

- The results of the analysis of the suicidal ideation and the level of oxytocin revealed that the patients with suicidal ideation had a lower oxytocin level compared to the depressed patients without suicidal ideation, which indicates a possible reveal of oxytocin as a marker of identification of the subjects the risk of suicide.

- It seems that in the case of depression accompanied by irritable colon there is a lower level of oxytocin concentration compared to patients with depression without irritable colon, which would suggest that oxytocin may mediate somatoform-like effects in the depression.

- In depression accompanied by irritable colon the level of cortisol increases proportionally with the level of oxytocin, which could indicate a relationship between these two systems in case of coexistence of the two pathologies.

Following the specific experiments on animal models of depression we can draw the following conclusions:

- For the forced swimming test, oxytocin administration determined an antidepressant effect demonstrated by a significant increase in mobility time compared to the control group, but also by a decrease in the floating time compared to the control group. Mobility time is an indicator of the fact that the animal does not give up, is looking for solutions to get rid of the stressful situation, and the increased mobility time in combination with oxytocin administration indicates an antidepressant effect of oxytocin.

- Oxytocin treatment of animals with depression resulted in a decrease in the latency time for the initiation of care or cleaning behavior. Low latency in the initiation of care is an indicator for the potential antidepressant effect of oxytocin

- During the three-room sociability test, we observed that oxytocin-treated animals spent more time in the living room and had a longer contact time with the unknown animals than with the familiar ones. Oxytocin-induced prosocial behavior is an indicator of antidepressant activity.

- Oxytocin administration had no effect on anxiety indicators assessed by caring behavior and immobility time in oxytocin-treated animals.

## III. Elements of originality

In the presented work, the studies carried out by the author bring a series of elements of originality, including:

1. It is the first doctoral work in the country conducted on the study of the relevance of oxytocin in affective disorders. Thus, within this approach, studies have been conducted to evaluate the concentration of endogenous oxytocin in major depression, as well as studies evaluating the antidepressant effects of exogenously administered oxytocin in experienced animals. To date, the role of the oxytocin system in depression is uncertain, but more and more research seems to support the importance of this molecule in various psycho-biological processes that are disturbed in a multitude of psychiatric disorders, including depression. Therefore, oxytocin is studied in many mental disorders, starting with autism, anxiety, depression, bipolarity but also in disorders of the schizophrenia spectrum in both humans and animal models.

2. The analysis of the importance of oxytocin in the affective depressive disorder was also performed by evaluating the oxytocin-cortisol relationship. This is particularly important since oxytocin has a modulatory role on cortisol. As far as we know, there are no studies to date on the relationship between oxytocin and cortisol in depression. We consider that the analysis of oxytocin as an impact that it can have in psychic disorders must be analyzed in relation to other molecules, because from the studies carried out so far, the oxytocin system seems to have a modulatory role, being influenced at the same time by other systems. of neurotransmission.

3. Oxytocin was also analyzed in the depression accompanied by a digestive functional disorder very often associated with depression in the clinic, irritable colon. This aspect was necessary to consider given the fact that oxytocin has both central and peripheral distribution, and these two distribution models appear to be interconnected. To analyze whether peripheral oxytocin is altered in depression accompanied by a functional digestive disorder, which has an important psychological component, we compared the level of peripherally measured oxytocin with the oxytocin level measured in patients with depression and without irritable bowel.

4. The analysis of antidepressant effects was also analyzed on animal models of depression, the present work being at the same time a translational research. Another novel aspect of this paper is the study of animal models of depression in which we analyzed the effects of oxytocin administration on behavioral indices relevant to depression. The necessity of this study results on the one hand from the difficulties of controlling the environmental factors in the case of studies on human subjects, which, as we know from the literature, can significantly change the level of oxytocin and cause errors

in interpreting the results and on the other hand, it is due to the difficulties of carrying out studies involving the administration of new substances in human subjects.

## III. Perspectives that open the thesis

The data obtained from these presented studies are especially relevant for completing the current knowledge about major depression and the oxytocin system. Currently, in Europe there is no approval for the exogenous administration of oxytocin in any psychiatric disorder, as is the case in the United States or Australia, and our study could open the line of research in this direction.

Another important aspect observed in our study is that depression accompanied by irritable colon, which is a functional digestive disorder commonly associated with depression, could be based on changes in the oxytocin system. New research on somatoform disorders, whether or not associated with depression, to include the relevance of oxytocin is encouraged. Thus, we identified changes in the level of oxytocin in severe depression and associated with irritable colon, which may reflect the importance of oxytocin in the etiopathogenic processes accompanying major depression, with manifestations of somatoform appearance, such as irritable colon.

Also, given the relationship between cortisol and oxytocin, it may be useful to identify these parameters and correct them in patients with depression but also in the event of association with somatoform digestive symptoms.

These data obtained in our research could explain at least in part how psychic processes are interlinked with their somatic reflection and may represent a starting point for further research on the connection between affective and digestive disorders.

Future research could analyze the effects of oxytocin and the dynamics of the cortisol-oxytocin relationship on somatoform digestive symptoms. Also, future studies could analyze the effects of oxytocin administration on depressive symptoms depending on the type and intensity of depression, as well as the presence or absence of related somatoform manifestations.

Beyond the aforementioned therapeutic perspectives, identifying a valid marker set for depression risk, depression prognosis or biological diagnosis of depression could in the future involve other biological indicators and oxytocin in relation to cortisol. Also, the identification of subjects who could respond to oxytocin treatment could be achieved by peripheral dosing, if other studies performed on a much larger population of subjects will confirm these results.

We expect from future research to analyze the relationship between the central oxytocin system and the peripheral oxytocin system in affective disorders, this aspect being particularly important for therapeutic perspectives.

Even though we are far from being able to make clinical recommendations regarding the use of oxytocin as a marker in depression / depression accompanied by irritable bowel, we believe that we have advanced our knowledge on this subject and hope that these studies will be a starting point for future studies.

## VI. Selective bibliographic references


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