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THE EFFECT OF TREATMENT WITH ATYPICAL ANTIPSYCHOTICS IN DEPRESSIVE DISORDER

PHD THESIS SUMMARY

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List of publications

Articles published in extenso as a result of doctoral research

1. Manea O, Bidian C, Moldovan R, Iliuță FP, Buduru AM, Mîrza TV, Manea M. Effect of paliperidone treatment and exercise in experimental depression. Health, Sports & Rehabilitation Medicine, 2019; 20(3):110-116.http://doi.org/10.26659/pm3.2019.20.3.110 .(articol cuprins în studiul 3)
2. Manea O, Bidian C, Moldovan R, Iliuță FP, Buduru AM, Mîrza TV, Manea M. The effect of paliperidone treatment and exercison the memory and learning ability in experimental depression. Health, Sports & Rehabil Med. 2019; 20(4):150-154. https://doi.org/10.26659/pm3.2019.20.4.150. (articol cuprins în studiul 3)
3. Manea O, Bidian C, Moldovan R, Iliuță FP, Buduru AM, Mîrza TV, Manea M,Ciobanu AM. The effect of combined antipsychotic antidepressant treatment in experimental depression Health Sports & Reabilitation Medicine 2020,21,3,155-162. https://doi.org/10.26659/pm3.2020.21.3.155 (articol cuprins în studiul 2 și 4).

1.1. General considerations

Depression is considered a mental disorder, which occupies an important place among both psychiatric and non-psychiatric disorders.

The World Health Organization estimates that depression affects about 121 million people and that by 2020 it will be ranked second in prevalence after cardiovascular disease. (1,2,3)

The disease can occur at any time of life, in childhood, adult life, the elderly life. The prevalence is 10-25% for women and 5-12% for men. The onset of major depressive disorder is 50% between the ages of 20 and 50, with an average onset of 40 years. Recent data indicate a decline in the onset, even at the age of 20. After 50-65 years, the rate of depression is equal for both genders.

The most affected population groups are the socio-professional active ones. (4)

Major depression is associated with a high suicide rate of 10-15%. (5)

1.2. Risk factors for depression

A number of depressive risk factors have been identified: depressive episodes in personal and hereditary antecedents, history of suicide attempts, female gender: it is 3 times more common in women than in men, onset under 40 years, non-specific chronic pain, postpartum period, with an incidence of 10-20% in women, sleep disorders, somatic comorbidities: cardiovascular disease, cerebrovascular disease, cancer, Parkinson's disease, Alzheimer's disease, rheumatoid arthritis, psoriasis, multiple sclerosis, type 2 diabetes, biorhythm disorders, metabolic syndrome (12-36%), lack of social support, occupational instability, recent negative life events: death of partner, accidents, divorce, smoking, alcohol and psychoactive substances (28-40%), physical inactivity , sedentary lifestyle, obesity, medication with depressant properties, cardiovascular preparations: reserpine, propranolol, methyldopa, clonidine, digitalis, diuretics thiazides, hormonal preparations: oral hormonal contraceptives, anabolic steroids, corticosteroids, psychotropics: benzodiazepines, neuroleptics, nonsteroidal anti-inflammatory drugs, immunomodulators: interferon. (4,6,7,8)

1.3. Etiopathogenesis of depression

Numerous depressants have been implicated in the etiopathogenesis of depression: anatomical, neurotransmitters, endocrine, neurotrophic, inflammatory, genetic, psychosocial, nutritional, seasonal. (4,7,9,10,11)

The biochemical hypothesis states that a series of small neurotransmitter molecules were involved in the etiopathogenesis of depression, based on animal studies, biological research and postmortem data, those identifying the mechanisms of action of antidepressants and evaluating neurotransmitter metabolites.

The neuroendocrine hypothesis is based on the activation / inhibition of some neuroendocrine axes, initiated from the level of the middle hypothalamus:

- hyperactivity of the hypothalamic-pituitary-adrenal cortex (HHCSR), with increased cortisol secretion
- decreased activity of the hypothalamic-pituitary-thyroid axis (HHTi), with low secretion of thyroid hormones
- decreased activity of the hypothalamic-pituitary-gonadal axis (HHGn) with low estrogen or testosterone secretion
- decrease in the secretion of pituitary somatotrophic hormone (STH) endocrine abnormalities: circadian rhythm for melatonin, prolactin. (7,9,12,13,14)

The stress hypothesis states that depression has involved a number of psychosocial and physical stressors, which can cause physiological, biochemical oxynitrosative (oxynitrosative stress), behavioral, and control strategies.

Depression has been associated mainly with mental and psychosocial stress: post-traumatic stress, future stress, over or under stress, somatopsychic and psychosomatic stress. (5,10,15,16,17)

The inflammation hypothesis describes the association of depression with increased susceptibility to infection, and immune activation is based on:

- hypersecretion of proinflammatory cytokines: IL-1, IL-8, IL-6, IL-10, TNF-α, INF-α;
- acute phase protein secretion: CRP;
- secretion of substance P, COX-2, PG-E2, lipoperoxides, sphingomyelin Z.

Depressogenic inflammatory mechanism is associated with hyperactivity of the hypothalamic-pituitary-adrenal cortex (4,7,8,18)

The neuroanatomical hypothesis suggests that depression was associated with a number of structures and 2 important neuroanatomical circuits: the cortico-thalamus-limbic circuit, which includes the prefrontal cortex, the mediodorsal thalamus, the limbic system,

the amygdala, and the hippocampal cortex; and the cortico-thalamus-pallido-striato-limbic circuit, which includes the prefrontal cortex, the mediodorsal thalamus, the globus pallidus, the striated bodies, and the hippocampus-amygdala complex. (7,19,20)

The genetic hypothesis considers that genetic factors have been implicated in depression, with varying weight, based on family studies of monozygotic and dizygotic twins and adoption studies. In bipolar disorder, several associated genomic regions were highlighted: JAM3 genes (chromosome 11q25), SLC39A3 (chromosome 19p13.3), ANK3 (chromosome 10q21), CACNA1C (chromosome 12p13.3), DGKH (chromosome 13q14). (5) In the genetics of unipolar depression, the main candidate gene involved is: CREB1 (chromosome 15q25). (5)

The hypothesis of seasonal variations suggests that depressive syndromes have been associated with lack of sun exposure and the winter season, with the involvement of seasonal factors and weather sensitivity being more pronounced in women. (21,22)

The neutrophic hypothesis is based on data on neurodegeneration caused by decreased neurotrophic factors: BDNF-brain-derived neurotrophic factor, erythropoietin, pituitary growth hormone, GDNF-glial cell line derived neurotrophic factor, which affects the hippocampus at the CA3 area causing atrophy, synapse plasticity, decreased neurogenesis and glycogenesis. (7,23,24,25)

The cognitive hypothesis considers depression as a cognitive disorder of negative self-perception, negative hostile perception of the present and future outside world, which causes self-restrictive behaviors, with cognitive and emotional deficit. (7,16,27)

The hypothesis of nutritional correlations attributes the appearance of depression to a vitamin nutritional deficiency (vitamin D, vitamins B2, B6 and B12, folic acid), omega 3 fatty acids and tryptophan. (9,23) The hypothesis of mineral homeostasis disorder associates depression with excess Zn, Al, Pb, Hg with neurotoxic role on the hippocampus. (9.28)

2. Experimental study of depression

2.1. General considerations

Depresia a fost studiată pe o serie de modele animale de rozătoare (șoareci și șobolani) și primate. Majoritatea studiilor s-au efectuat pe șobolani, având în vedere: condițiile de vivarium adecvate și riguros controlate, durata medie de viață și corespondența cu vârsta umană (2 ani corespunde la șobolani, vârstei umane de 60 ani), caracteristicile temporare ontogenetice ale dezvoltării cerebrale, sistemul nervos mai simplu, omogenitatea genetică, monitorizarea factorilor de risc, comportamentul locomotor și psihoemoțional mai ușor de interpretat, posibilitatea unui număr mare de intervenții. (9,29,30,31)

Experimental models of depression are divided into genetically selected animal models (9,32): Wistar-Kyoto rats, Flinders line rats, Fawn-Hooded rats, behaviorally anxious rats, spontaneously hypertensive rats, Floripa H and L line rats, Lewis rats , rats with congenital helplessness and animal models with induced depression (9,31,33,34): Of which we note, surgically induced depression by: olfactory bulbectomy, traumatic brain injury, occlusion of the cerebral artery, intracranial self-stimulation and pharmacologically induced depression : administration of depressants such as dexamethasone, reserpine, aldosterone, endothelin I, delta (9) -tetrahydrocannabinol, corticosterone, titanium dioxide nanoparticles, drug withdrawal, acute and chronic stress procedures through :, social and maternal isolation, immobilization, trauma , sleep deprivation, conflict stress, unpredictable stress, uncontrollable, wheel-lock pattern, tumor induction.

2.3. Objective diagnosis of depression in animals (27)

Several specific tests are used in rats:

- sucrose test for anhedonia (hyposensitivity to olfactory stimuli - major symptom of depression in rats)

- tail suspension test for antidepressant activity

- Open-Field test, for emotion and involuntary locomotor activity

- Morris water maze test for motor learning and memory.

3. Neurobiological models of depression used in the thesis

3.1. Rezerpine-induced depression model

Rezerpine has been used as a pharmacological agent inducing depression. Rezerpine is the main alkaloid extracted from the root of Rauwolfia serpentina plant, native to India, Indonesia, Ceylon, Malaysia, Central Africa, Central and South America. but also peripheral, disrupting the metabolism of endogenous biogenic monoamines: norepinephrine, dopamine and serotonin. The tranquilizing effect occurs 40-60 minutes after administration. Long-term administration has cumulative, antipsychotic effects.

The use of Rezerpine in the form of various preparations (Raunervil +, RausedylR, ReserpinR SerpasilR) in the treatment of essential hypertension is limited by the state of severe depression which it may cause. It is recommended only in psychoses accompanied by hypertension. The observation is based on the experimental use of Rezerpine to induce depression.

Depression was induced by the pharmacological methods with Rezerpine (DIR) administered 1 mg / kg body weight / 24 h i.p. 4 days (42.43)

Personal Research

1. Objectives

1.1. The general objective

Study, on an experimental model of rat-induced depression, of the effects of: atypical antipsychotics, increased antidepressant treatment, associated with atypical antipsychotics, co-treatment with antidepressants, and atypical antipsychotics and Omega-3 polyunsaturated fatty acids, antipsychotic treatment atypical associated with antidepressants and physical exertion.

1.2. Specific objectives

The effects of therapy will be monitored on: motor and exploratory behavior, emotional behavior, motor learning and memory.

2. General methodology

The studies were performed on white male rats, Wistar breed, aged 4 months, weighing 200-250 grams, from the Biobase of the University of Medicine and Pharmacy "Iuliu Haţieganu" Cluj-Napoca.

The animals were kept throughout the studies in adequate vivarium conditions: temperature, humidity, lighting, feeding and hydration.

Research calendar by objectives, days (T) and study methods, included:

2.1. Inducerea depresiei

Rezerpine has been used as a pharmacological agent inducing depression. Rezerpine is the main alkaloid extracted from the root of Rauwolfia serpentina. It has a predominantly central tranquilizing, antidepressant, but also peripheral action, to disrupt the metabolism of endogenous biogenic monoamines: norepinephrine, dopamine and serotonin. The tranquilizing effect occurs 40-60 minutes after administration. Long-term administration has cumulative, antipsychotic effects.

Depression was induced by the pharmacological method with Rezerpine (DIR) administered 1 mg / kg body weight / 24 h i.p. 4 days (42.43)

2.2.Depression control

The Tail Suspension (TST) test was used to measure depression (44).

The tail suspension test is one of the most widely used tests for assessing antidepressant activity in rodents. The test is based on the fact that animals subjected to short-term stress, from which they cannot escape, being suspended by their tails, will adopt an immobile position. Immobility is defined as the absence of voluntary movements and includes passive balance.

The duration of the test was 6 minutes, the immobilization time being recorded with a stopwatch. After initial movements (attempts) to escape, the suspended rat adopts an immobile position, alternating with periods of agitation. The total duration of the immobilization is calculated as the time when the force of movement of the animal is below a predetermined threshold.

If an animal raises its tail, it is slowly pulled back and the test continues. Rats, which raise their tails for more than 20% of the test duration (72 sec), are eliminated from the final assessment. Values are expressed in seconds.

Interpretation: Prolonged suspension time means anxiety and depression in the animal.

2.3.Treatment program

-monotherapy with antipsychotics 14 days, quetiapine (QUE): 5mg / kg body weight / 24 h i.p., aripiprazole (ARI): 1.5mg / kg body weight / 24h i.p., paliperidone (PALI): 0.5mg / kg body weight / 24 h Ip

-co-treatment with antipsychotics and antidepressants 14 days QUE 5mg / kg body weight / 24h i.p. + Agomelatine (AGO) 1mg / kg body weight / 24 h i.p., ARI 1.5 mg / kg body weight / 24h i.p. + Escitalopram (ESC) 0.5 mg / kg body weight / 24 h i.p.

-treatment with antipsychotics and physical exertion by swimming test, for 14 days QUE 5mg / kg body weight / 24 h i.p. + effort, ARI 1.5 mg / kg body weight / 24h i.p. + effort, PALI 0,5mg / kg body weight / 24 h i.p. + effort

-co-treatment with antipsychotics, antidepressants and omega 3 fatty acids (AG omega 3), for 14 days administered by oropharyngeal gavage, for 14 days QUE 5mg / kg body weight / 24h i.p. + AGO 1mg / kg body weight / 24 h i.p + AG omega 3 30mg / kg body weight / 24 h body weight, ARI 1.5 mg / kg body weight / 24 h i.p. + AGO 1mg / kg body weight / 24h i.p. + AG omega 30mg / kg body weight / 24 h body fat, QUE 5mg / kg body weight / 24 h i.p + ESC 0.5 mg / kg body weight / 24 h i.p. + AG omega 3 30mg / kg body weight / 24 h body fat, ARI 1.5 mg / kg body weight / 24 h i.p. + ESC 0.5 mg / kg body weight / 24 h body weight + AG omega3 30 mg / kg body weight / 24 h body fat (45)

2.4. Therapy control

a. Open Field Test (OFT) (after Denenberg and Whimby, 1963), for testing involuntary mobility: spontaneous locomotor behavior, hyperactivity, exploratory behavior in open space, and induced anxiety. (45)

It is a test used in laboratory rodents and designed to measure behavioral responses: emotionality, spontaneous motor activity, hyperactivity and outdoor behavior in the open. The test is also used to measure anxiety. In the 300W illuminated experimental space, the open but delimited field acts at the same time as an anxious stimulus, the test being to measure the anxiety induced based on the locomotor activity and the exploratory behavior in animals.

The test of emotion and motility was performed in the open field cylinder (after Denenberg and Whimby, 1963) (45). The exploration space was cylindrical, with a radius of 50 cm, a height of 100 cm, the duration of the test being 3 minutes.

The monitored indicators were emotion and motility. Emotion was calculated based on the emotional score (SE): the sum of urination and defecation expressed in absolute values. Spontaneous motility was calculated based on the motility score (MS): the sum of crossings from one sector to another and the rearing of two paws.

Interpretation of indicators: the increase in the number of urination and defecation is considered an indicator of emotion. Increased spontaneous motility is considered an indicator of a lack of anxiety.

Morris test for spatial motor learning and memory testing (46)

Testul Water Maze Morris (WMM) (testul labirintului Morris în apă) (după Morris 1981)(46)

The Morris water maze is a metal cylinder with a diameter of 62 centimeters and a height of 49 centimeters, divided into four quadrants, called A, B, C, D. The device fills with water, and by adding kaolin, the water becomes cloudy, preventing it from being seen underwater. In one of the dials (D), a platform is inserted immediately below the surface of the water (2 cm), but which cannot be visualized by the experimental animal, the water being cloudy, due to the presence of kaolin. The water temperature is maintained at 25-27 0C. The experiment lasts 4 days, 3 days being training and the 4th day is testing.

The fourth day is the testing day. The platform is removed from the D dial. Each experimental animal is subjected to a single test, lasting 1 minute, being released from the dial following the last training dial of the previous day. Note the time elapsed until the animal reaches the D quadrant, noted as the latency time, as well as the total time of the 60 seconds spent in the D quadrant in search of the platform. The number of complete laps that the animal performs in quadrant D, around the place where the platform was located, is also quantified.

2.5. Group

L I-control animals - control at which saline 5ml / kg body weight / 14 days is administered

L II-animals with reserpine-induced depression (DIR)

L III-animal DIR + QUE

L IV-animal DIR + ARI

L V-animal DIR + PALI

LVI-animal DIR + QUE + AGO

LVII-animal DIR + QUE + ESC

LVIII-animal DIR + ARI + AGO

L IX-animals DIR + ARI + ESC

LX-animal DIR + QUE + effort

LXI-animals DIR + ARI + effort

LXII-animals DIR + PALI + effort

LXIII-animal DIR + QUE + AGO + AG omega 3

LIV-animal DIR + ARI + AGO + AG omega3

LXV-animal DIR + QUE + ESC + AG omega 3

LXVI-animal DIR + ARI + ESC + AG omega 3

2.6.Statistical analysis

Elements of descriptive statistics were calculated and the data were presented using indicators of centrality, location and distribution.

For the statistical analysis of the data, in the case of data with normal distribution, the Student's test was used for independent samples, the variations being tested with the Levene test for variation. The Kolmogorov-Smirnov test was used to test the normal distribution. In the case of unevenly distributed values, the Student's test was replaced by the non-parametric Mann-Whitney (U) test for two unpaired samples.

The significance threshold for the tests used was $\alpha = 0.05$ (5%), as follows:

- $0.01 < p < 0.05$-statistically significant difference;

- $0.001 < p < 0.01$- statistically very significant difference;

- $p < 0.001$- highly significant difference;

- $p > 0.05$- statistically insignificant difference.

The Bravais-Pearson correlation coefficient (r) was used to detect the correction between two continuous quantitative variables with normal (uniform) distribution. In the case of variables with uneven distribution, the rank correlation coefficient was used

Spearman (ρ). The analysis of the correlation coefficients was performed using Colton's rule. Thus, starting from the properties of the correlation coefficient that say that this is a number between -1 and 1 and that the "intensity" of the linear relationship between the two variables will be even higher as the correlation coefficient approaches 1 in value. Colton (1974) (47) suggested the following empirical rules for interpreting the correlation coefficient:

- weak / zero correlation, if r ∈ [-0.25, +0.25] - noted *
- acceptable correlation, if r ∈ [+ 0.25, + 0.5] U [-0.5, -0.25] -noted **
- good correlation, if r ∈ (+ 0,5, + 0,75] U [-0,75, -0,5) -notated ***
- very good correlation, if r ∈ (+ 0.75, + 1] U [-1, -0.75) -noted ****

Elements of descriptive statistics were calculated, the data being presented using indicators of centrality, location and distribution.

3. Study 1. The effect of treatment with atypical antipsychotics in experimental depression

3.1 Objectives

We aimed to study the effects of atypical second-generation antipsychotics - Quertiapine, Aripiprazole, and Paliperidone - on an experimental model of induced depression in rats, on emotional and locomotor behavior and motor learning, and learning and control.

3.2. Materials and methods

3.2.1. Groups

The groups were composed of 10 white, male rats, Wistar breed weighing 150-200 grams, groups I, II, III, IV, V as specified in Chapter 2.3.

3.2.2. Methods

1) Induction of depression was performed according to the experimental protocol, chapter 2, subchapter 2.1 .;

2) Determination of depression and anxiety by TST, according to subchapter 2.2., Chapter 2;

3) Determination of emotivity and spontaneous locomotor activity by OFT, according to subchapter 2.4., Chapter 2;

4) determination of motor learning ability and memory based on the WMM test, according to subchapter 2.4., Chapter 2;

3.2.3.Statistical processing

The statistical processing was performed according to the procedures described in subchapter 2.6 chapter 2 “General methodology”.

3.4 Results

3.4.1. Tail suspension test (Table I, Figure 1)

In the statistical analysis of the values of the tail support test (TST), they were observed: taking into account the 5 groups of rats studied, at time T0 - lack of statistically significant differences between groups ($p > 0.05$), at time T14 and T30 - statistically significantly significant between at least two of the groups ($p < 0.001$), taking into account the 3 time points studied, in group I - lack of statistically significant differences between the time moments studied ($p > 0.05$), in groups II, III, IV and V - statistically significantly significant differences between at least two of the time points ($p < 0.001$).

In the statistical analysis of TST values, were observed for unpaired samples: at time T0 - lack of statistically significant differences between groups ($p > 0.05$), at time T14 - statistically significant differences between groups III-IV ($p < 0, 05$) and statistically significant differences between groups I-II, I-III, I-IV, I-V, II-III, II-IV, III-V, IV-V ($p < 0.001$), at time T30 - statistically different significant differences between groups III-V ($p < 0.05$) and statistically significant differences between groups I-II, I-III, I-IV, I-V, II-III, II-IV, II-V, III-IV, IV-V ($p < 0.001$).

In the statistical analysis of TST values, were observed for paired samples: in group I - lack of statistically significant differences between time moments ($p > 0.05$), in group II - very statistically significant differences between T0-T14, T14- T30 ($p < 0.01$) and statistically significant differences between T0-T30 ($p < 0.001$), in group III - statistically significant differences between T0-T14, T0-T30, T14-T30 ($p < 0.001$), at group IV - very statistically significant differences between T0-T14, T0-T30, ($p < 0.01$), in group V - statistically significant differences between T14-T30 ($p < 0.05$), very statistically significant differences between T0- T30 ($p < 0.01$) and statistically significant differences between T0-T14 ($p < 0.001$).

3.4.2. Open-Field Test (Tables II a, II b, III, IV, Figures 2 and 3)

In the statistical analysis of the values of the Open Field test - emotion score, taking into account the 4 groups of rats studied (without the control group) were observed statistically significant differences between groups at time T0 ($p < 0.05$) and statistically significant differences between groups at times T14 and T30 ($p < 0.0001$).

In the statistical analysis of the values of the Open Field test - motility score, taking into account the 4 groups of rats studied (without the control group), statistically significant differences were observed between groups at times T0, T14 and T30 ($p < 0.0001$).

In the statistical analysis of the values of the Open Field test for unpaired samples, they were observed for:

Emotivity score: at time T0 - statistically significant differences between groups I-III, II-III, III-IV, III-V ($p < 0.05$), at time T14 - very statistically significant differences between groups III-V ($p < 0.01$) and statistically significant differences between groups I-II, I-IV, I-V, II-III, II-V, III-IV, IV-V ($p < 0.001$), at time T30 - statistically different significant differences between groups I-II, III-IV ($p < 0.05$), very statistically significant differences between groups I-V ($p < 0.01$) and statistically significant differences between groups I-IV, II-IV, III-IV , IV-V ($p < 0.001$).

Motility score: at time T0 - statistically significant differences between groups I-III, I-IV, II-III, II-IV, III-V, IV-V ($p < 0.001$), at time T14 - statistically very differences significant differences between groups III-IV ($p < 0.01$) and statistically significant differences between groups I-II, I-IV, I-V, II-III, II-IV, III-V, IV-V ($p < 0.001$) , at time T30 - statistically significant differences between groups III-IV ($p < 0.05$), very statistically significant differences between groups I-V, II-III ($p < 0.01$) and statistically significant differences between groups I-II, I-III, I-IV, II-V, III-V, IV-V ($p < 0.001$).

In the statistical analysis of the values of the Open Field test for paired samples (T0-T14, T0-T30, T14-T30), they were observed for:

Emotivity score: in group II - statistically significant differences between T0-T30 and T14-T30 ($p < 0.05$) and statistically significant differences between T0-T14 ($p < 0.001$), in group III - lack of statistically significant differences between the 3 time points ($p > 0.05$), in group IV - very statistically significant differences between T0-T14 ($p < 0.05$) and statistically significant differences between T0-T30 ($p < 0.001$), in group IV V - statistically significant differences between T0-T14 and T0-T30 ($p < 0.001$).

Motility score: in group II - intensely statistically significant differences between T0-T14, T0-T30 and T14-T30 ($p < 0.001$), in group III - very statistically significant differences between T0-T14 and T0-T30 ($p < 0 .01$) and statistically significant differences between T14-T30 ($p < 0.001$), in group IV - statistically significant differences between T0-T14, T0-T30 and T14-T30 ($p < 0.001$), in group V - statistically significant differences significant differences between T14-T30 ($p < 0.05$) and statistically very significant differences between T0-T14 and T0-T30 ($p < 0.01$).

Statistical analysis of the correlation between the values of the tail support test and the scores of emotion (SE) and motility (MS) showed: at time T14 - negative correlation acceptable with MS at lotuV ($p > 0.05$), and at time T30 - very good negative correlation with SE in group II ($p < 0.01$), good negative correlation with SE in groups III and V ($p < 0.05$), positive positive correlation with MS in groups III and V ($p > 0, 05$).

In the statistical analysis of the Morris test values, the following were observed:

considering the 4 groups of rats studied (without the control group) in the learning period at T14 and T30 - statistically significant differences between at least two of the groups ($p < 0.001$) taking into account the 4 groups of rats studied (without control group) during the control period at T14 and T30 - statistically significant differences between at least two of the groups ($p < 0.001$).

3.4.3. Morris test (Table V, Figure 4)

In the statistical analysis of the values of the Morris test during the learning period, they were observed for unpaired tests: at the time of T14 - statistically significantly significant differences between groups I-II, I-III, I-IV, I-V, II-IV, III-IV , IV-V ($p < 0.001$) and statistically very significant differences between groups II-V, III-V ($p < 0.01$), at time T30 - statistically significant differences between groups I-II, I-III, I -IV, I-V, II-V, III-V, IV-V ($p < 0.001$), statistically very significant differences between groups II-IV ($p < 0.01$) and statistically significant differences between groups II-III ($p < 0.05$).

In the statistical analysis of Morris test values during the control period, they were observed for unpaired samples: at time T14 - statistically significant differences between groups I-II, I-III, I-IV, I-V, II-IV, II-V , III-V, IV-V ($p < 0.001$), at time T30 - statistically significant differences between groups I-II, I-III, I-IV, I-V, II-IV ($p < 0.01$), differences statistically significant differences between groups II-III, II-V ($p < 0.05$) and statistically significant differences between groups IV-V ($p < 0.05$).

In the statistical analysis of the Morris test values, statistically significant differences for group V ($p < 0.001$) and statistically very significant differences for group II ($p < 0.001$) were observed for the pair samples between T14-T30 <0.01) and statistically significant differences for group V ($p < 0.001$).

In the statistical analysis of Morris test values, they were observed for paired samples between the learning period and the control period: for group II - very statistically significant differences ($p < 0.01$) at times T14 and T30, and for groups III, IV and V - statistically significant differences ($p < 0.001$) at T14 and T30.

3.5. Conclusions

1. The experimental model of rezerpine-induced depression is characterized by increased emotionality and anxiety, increased emotionality and decreased locomotor activity, decreased learning ability, and memory.

2. The administration of QUE to depressed animals causes, compared to untreated depressive animals, an increase in emotion, an increase in exploratory locomotor activity, an increase in learning capacity and memory capacity.

3. The administration of ARI to depressed animals causes, compared to untreated depressive animals, increases in emotionality, decreases in emotionality, increase in learning capacity and memory capacity.

4. The administration of PALI to depressed animals causes, compared to untreated depressive animals, decreases in emotion and anxiety, increases in involuntary motility and increases in learning and memory capacity.

5. The administration of atypical PAs in animals with experimental depression significantly influences the learning and control process, the values being maximum after the treatment with PALI and ARI.

4. **Study 2. The effect of co-treatment with atypical antipsychotics and antidepressants in experimental depression**

4.1. Objectives

The aim of the study was to follow on an experimental model of rat-induced depression the effect of AGO and ARI co-treatment on emotional and exploratory motor behavior and motor and memory learning.

4.2. Materials and methods

4.2.1.Groups I, II, III, IV, VI, VII, VII, IX in which rezerpine was administered as a preparation Reserpinum Sigma, QUE as a preparation SeroquelR, Astra ZenecaR UK Limited, AGO as a preparation Valdoxan produced by Les Laboratoires Servier, ESC as a Cipralex preparation produced by Lundbeck-concerned

4.2.2 Methods

1) Induction of depression was performed according to the experimental protocol, chapter 2, subchapter 2.1 .; Determination of TST anxiety according to subchapter 2.2. chapter 2;

3) determination of spontaneous locomotor emotion and activity by OFT, according to subchapter 2.4., Chapter 2;

4) determination of motor learning ability and memory based on the WMM test, according to subchapter 2.4., Chapter 2;

4.2.3.Statistical processing

The statistical processing was performed according to the procedures described in subchapter 2.6 chapter 2 "General methodology".

4.3.Results

4.3.1 Effect of Quetiapine and Agomelatine on Experimental Depression

In group VI, with experimental depression induced with reserpine, the co-treatment with QUE and AGO determines: at TST compared to group III, treated with QUE, very significant decreases of values in T14 and T30, compared to the initial values; at OFT the score of emotion, compared to group III treated with QUE very significant decreases in values in Q14 and Q30 and at the same time, compared to the initial values; at OFT the motility score, very significant increases in T14 compared to the group treated with QUE and in the moments T14 and T30, compared to the initial values; in the Morris test for learning, compared to group III, treated with QUE very significant decreases in values in T14 and T30, and significant increases in T14 and T30 compared to the control; in the Morris test for learning control, very significant decreases in T30 and compared to the control group T14 and T30;

Compared to group II in induced depression (DIR) and untreated, the treatment of QUE and AGO determines: at TST: very significant increases in values in T14; at OFT emotion score: very significant decreases in values at T14 and T30; at OFT motility score: very significant decreases in values at T14 and T30; Morris test for learning: very significant decreases in values at T14 and T30; in the Morris test for learning control: very significant decreases in values at T14 and T30;

4.3.2. Effect of Quetiapine and Escitalopram on Experimental Depression In group III with rezerpine-induced experimental depression, co-treatment with QUE and ESC results in: at TST, compared to the group treated with QUE, significant decreases in values at T14 and T30 and very significant increases in values at T14 and T30 compared to initials; at OFT the score of emotion, compared to the group treated with QUE very significant decreases in values at T14 and T30 and at T30 compared to the initial values; at OFT, the motility score, compared to the group treated with QUE, very significant increases in values at T30 and at times T14 and T30 compared to the initial values; in the Morris test for learning, compared to the group treated with QUE very significant decreases at times T14 and T30 and significant increases compared to controls at times T14 and T30; in the Morris test for

learning control, compared to the group treated with QUE very significant decreases in T14 and T30 and significant decreases compared to controls at time T14.

Compared to group II with induced and untreated depression, the QUE and ESC co-treatment causes: at TST very significant decreases of values in T14 and T30; at OFT - emotion score very significant decreases in values in Q14 and Q30; at OFT -motility score very significant decreases in values in T14 and T30; in the Morris test - learning score very significant decreases in values in T14 and T30; Morris test for learning control very significant decrease in values in Q14;

4.3.3. The effect of Aripiprazole and Agomelatine on experimental depression

In group VIII with induced experimental depression, co-treatment with ARI + AGO causes: in TST, compared to group IV treated with ARI, very significant decreases in values in T14 and T30 and very significant increases in values in T14 and T30; at OFT - the score of emotion, compared to group IV, very significant decreases of values in T14 and T30 and at the same moments, compared to the initial values; at OFT-motility score, compared to group IV very significant increases in values in T14 and T30 and at the same times compared to the initial values; in the Morris test for learning, compared to group IV very significant decreases in values in T14 and T30 and very significant increases at the same time, compared to controls; in the Morris test for learning control, compared to group IV very significant decreases in values in T14 and T30 and at the same time, compared to controls;

Compared to group II with induced depression, the ARI + AGO co-treatment determines: at TST, very significant decreases at T30; at OFT IV emotion score very significant decreases in values in Q14 and Q30; at OFT motility score, very significant increases in values in Q14 and significant decreases in values in Q30; Morris test for learning, very significant decreases in T14 and T30; Morris test for learning control, very significant decreases in T14 and T30;

4.3.4. Effect of Aripiprazole and Escitalopram on Experimental Depression

In group IX, with experimental depression induced with reserpine, the co-treatment of ARI and ESC determines: in TST, compared to group IV, very significant decreases in the T14 and T30 moments and very significant increases in the same moments, compared to the initial values; at OFT-the score of emotion, compared to group IV, insignificant changes and very significant decreases in the moments T14 and T30, compared to the initial values; at OFT the motility score compared to group IV, very significant increases at times T14 and T30 and compared to the initial values; in the Morris test for learning, compared to group IV, very significant decreases at times T14 and T30 and very significant increases compared

to the control; in the Morris test for learning control compared to group IV very significant decreases at times T14 and T30 and at the same times compared to controls.

Compared to group II with induced depression (DIR), the ARI + ESC co-treatment determines: at TST very significant decreases in T30; at OFT emotion score, very significant decreases in T14 and T30; at OFT motility score, very significant decreases in T14 and very significant increases in T30; at the Morris test for learning, very significant decreases in T14 and T30; Morris test for learning control, very significant decreases in T14 and T30;

4.4. Conclusions

1. The groups receiving treatment with atypical antipsychotics and antidepressants show relief from depression and anxiety, decreased emotionality and spontaneous motility, and increased learning and control of untreated depressive animals.

2. The administration of QUE and AGO, causes compared to the group treated with QUE, very significant decreases in emotion and anxiety, significant increases in spontaneous motility, significant increases in learning and control capacity at times T14 and T30.

3. The administration of QUE and ESC causes, compared to the group treated with QUE, very significant decreases in emotion and anxiety, significant increases in spontaneous motility, significant increases in learning and control capacity at times T14 and T30.

4. The administration of ARI and AGO causes, compared to the group treated with ARI, very significant decreases in emotion and anxiety, significant increases in spontaneous motility, significant increases in learning capacity and decreases in control learning control at T14 and T30.

5. The administration of ARI and ESC causes, compared to group IV treated with ARI, very significant decreases in emotion and anxiety, very significant increases in spontaneous motility, very significant increases in learning and control capacity at T14 and T30.

5. Study 3. The effect of treatment with atypical antipsychotics and physical exertion on experimental depression

5.1.Objectives

We aimed to study the effects of atypical PA, ARI along with PALI in depressed animals subjected to physical exertion by swimming test, on emotional behavior, exploratory locomotor, motor learning and memory.

5.2. Material and methods

5.2.1. Groups I, II, III, IV, V, X, XI, XII

The preparations used were: QUE used was the preparation SeroquelR produced by Astra ZenecaR UK Limited, ARI used was the preparation Ability and PALI used was the preparation InvegaR Janssen-Cilag SpA, Italy.

5.2.2. Methods

1) The induction of depression was performed according to the experimental protocol, chapter 3, subchapter 3.1.;

2) Determination of anxiety by TST, according to subchapter 3.2., Chapter 3;

3) Determination of emotivity and spontaneous locomotor activity by OFT, according to subchapter 3.4., Chapter 3;

4) Determination of motor learning ability and memory based on the WMM test, according to subchapter 3.4., Chapter 3;

5) The physical exercise test after Nayatanara et al (84) consisted of the swimming test for one hour daily, in a plastic pool, with water thermostated at 200C, dimensions 100 cm long, 60 cm high, level water 30 cm. The value of the effort capacity, in seconds, was calculated by timing the time interval from the introduction of the animals in the pool. The duration of the effort was 30 minutes.

5.2.3. Statistical processing

The statistical processing was performed according to the procedures described in subchapter 3.6 chapter 3 "General methodology"

5.3 .Results.

As the results for groups I, II, III, IV and V were presented in study I, the results for groups X, XI and XII as well as the comparative results between groups I-V and X, XI and XII will be presented below.

Effect of Quetiapine on Experimental Depressed Animals.

In group X with experimental depression induced with reserpine, treatment with QUE and physical exertion determine: at TST - very significant increases in values at T14 and T30, compared to baseline T0, compared to control values L I, compared to untreated animals L II and compared to sedentary treated animals L III very significant decreases, at OFT the score of emotion: very significant decreases in the moments T14 and T30, compared to the initial values from the moment T0 and compared to the control values L I; compared to the values of untreated animals L II at the same time and to the values of sedentary treated animals LIII; at OFT the motility score very significant increases at times T14 and T30, compared to the initial values at time T0, very significant decreases compared to the control values L I at times T14 and T30; very significant decreases at times T14 and T30 compared

to the values of untreated animals L II and very significant increases at the same times compared to the values of sedentary treated animals LIII; in the Morris test for learning: very significant increases in values at time T14, compared to control values L I, compared to untreated animals L II at times T14 and T30 and at the same time, compared to values of sedentary treated animals LIII; in the Morris test for learning control very significant decreases in T14 and T30, compared to control values L I, compared to untreated animals L II in T14 and T30 and at the same time compared to the values of sedentary treated animals LIII;

The effect of Aripiprazole on animals with experimental depression under physical exertion

In group XI with rezerpine-induced experimental depression, ARI treatment and physical exertion determine: values of sedentary animals treated L IV at times T14 and T30; at OFT the score of emotion very significant decreases of the values in the moments T14 and T30 compared to the initial values T0, compared to the control values L I and compared to the values of the untreated animals L II and sedentary treated L IV at the same moments; at OFT the motility score very significant increases in values at times T14 and T30, compared to the initial values T0, compared to the control values L I, compared to the values of untreated animals L II at time T30 and compared to the values of sedentary animals treated L IV at times T14 and T30; in the Morris test for learning very significant increases compared to the control values L I at times T14 and T30 and compared to the values of untreated animals L II at the same times; compared to the values of animals treated sedentary at times T14 and T30; in the Morris test for learning control, very significant decreases in values at times T14 and T30, compared to the control values L I at the same times and compared to the values of animals treated sedentary at times T14 and T30;

The effect of Paliperidone on animals with experimental depression, subjected to physical exertion

In group XII with experimental depression induced with reserpine, treatment with PALI and physical exertion determine: at TST - very significant increases in values at times T14 and T30 compared to the initial values T0, compared to control values L I at the same times the values of sedentary animals treated LV at the same time; at OFT the score of emotion: very significant increases in values at T14 and T30 compared to the initial values T0, compared to the values of the control group L I at T14, very significant decreases at T30 compared to the values of sedentary animals treated LV; at OFT the motility score: very significant decreases at time T14 compared to the initial values T0, insignificant changes at

times T14 and T30 compared to the values very significant increases of at times T14 and T30 compared to the values of sedentary animals treated LV; in the Morris test for learning: very significant increases in T14 and T30 compared to the control values L I, compared to the untreated group at T30 and in T14 and T30 compared to the values of sedentary animals treated LV; in the Morris test for learning control: very significant decreases in values at T14 and T30, compared to control values L I and the untreated group and significant increases at T30 compared to the sedentary group treated LV;

5.4.Conclusions:

1. The administration of Quetiapine to animals with experimental depression subjected to physical exertion causes a decrease in anxiety and depression, emotion, increased spontaneous motility, increased learning and memory capacity, compared to treated sedentary animals.

2. The administration of Aripiprazole to animals with experimental depression subjected to physical exertion causes a decrease in anxiety and depression, emotion, increased spontaneous motility, increased learning and memory capacity, compared to treated sedentary animals.

3. Administration of Paliperidone to animals with experimental depression subjected to physical exertion causes a decrease in anxiety and depression, emotion, increased spontaneous motility, increased learning and memory capacity, compared to treated sedentary animals.

4. The administration of atypical antipsychotics to animals with experimental depression subjected to physical exertion has favorable effects in the treatment of depression, the best effects being after the treatment with Paliperidone.

6. **Study 4. Effect of co-treatment with antipsychotics, antidepressants and omega 3 fatty acids in experimental depression**

6.1. Objectives

We aimed to study on an experimental animal model of depression the effects of atypical PAs associated with AD and AGPN-omega 3 on emotional behavior, exploratory locomotor, motor learning and memory.

6.2.Material and methods

6.2.1.Groups. The groups consisted of 10 white, male Wistar rats weighing 150-200 grams, Groups XIII, XIV, XV, XVI

The preparations used were: SeroquelR Astra ZenecaR UK Limited. The ARI used was Ability. AGO preparation Valdoxan, Les Laboratories Servier, ESC preparation

Cipralex produced by Lundbeck-concern and AGPN-Omega 3 from Ozone Laboratories Pharma S.A.

6.2.2.Methods

1) Induction of depression was performed according to the experimental protocol, chapter 2, subchapter 2.1 .;

2) Determination of anxiety by TST, according to subchapter 2.2., Chapter 2;

3) Determination of emotivity and spontaneous locomotor activity by OFT, according to subchapter 2.4., Chapter 2;

4) Determination of motor learning ability and memory based on the WMM test, according to subchapter 2.4., Chapter 2;

6.2.3.Statistical processing

The statistical processing was performed according to the procedures described in subchapter 3.6 chapter 3 "General methodology".

6.3.Results of the study IV

As the results for groups I and II were presented in study I and those for groups VI, VII, VIII and IX in study II, the results for groups XIII, XIV, XV and XVI as well as the comparative results will be presented below. between groups I, II, VI-IX and XIII, XIV, XV and XVI.

Effect of administration of Quetiapine, Agomelatine and Omega 3 polyunsaturated fatty acids on animals with experimental depression (group XIII)

At TST- very significant increases compared to the initial values T0, compared to the control values LI, very significant decreases compared to the values of treated animals (L IV) and compared to the values of untreated depressive animals L II, at times T14 and T30.

At OFT-score emotion: very significant decreases compared to the initial values T0 and compared to the control values L I at times T14 and T30 compared to the values of untreated depressive animals L II and insignificant changes compared to the values of treated depressed animals L VI.

At OFT-motility score: very significant decreases compared to the control values L I at times T14 and T30, very significant increases compared to the initial values T0 at times T14 and T30, very significant increases compared to T30, compared to the values of untreated depressive animals L II; , very significant increases at T14 and T30, compared to the values of treated depressed animals L VI.

In the Morris test for learning: very significant increases at T14 compared to control LI values and very significant decreases at T14 and T30 compared to the values of untreated depressive animals L II, very significant decreases at T30 compared to the values of treated animals L VI.

In the Morris test for learning control: significant decreases in values at T14 and T30 compared to controls L I, compared to the values of untreated animals L II and compared to those treated L VI.

Effect of administration of Aripiprazole, Agomelatine and Omega 3 fatty acids on animals with experimental depression (group XIV)

At TST: very significant increases compared to the initial values T0, compared to the control values LI at times T14 and T30 and very significant decreases at times T14 and T30 compared to the values of untreated depressive animals L II and treated L VIII.

At OFT-emotion score: very significant decreases compared to the initial values T0 at times T14 and T30 and compared to the control group L I at the same times; very significant decreases at times T14 and T30 compared to the untreated group L II and insignificant changes compared to the treated group L VIII;

In the Morris test for learning: very significant increases at times T14 and T30, compared to the control values LI and compared to the treated group L VIII; very significant decreases in values compared to the untreated group L II at times T14 and T30.

In the Morris test for learning control: very significant decreases in values at times T14 and T30 compared to controls L I and compared to the untreated group L II, significant decreases at time T30, compared to the treated group L VIII;

Effect of administration of Quetiapine, Escitalopram and Omega 3 fatty acids on animals with experimental depression (group XV).

At TST: very significant increases at times T14 and T30, compared to the initial values T0 and compared to the control group L I; very significant decreases compared to the values of untreated depressive animals L II and treated with QUE and ESC in group VII values at times T14 and T30;

At OFT-emotion score: very significant decreases in moments T14 and T30 compared to T0 values and compared to controls L I; very significant decreases compared to the values of untreated depressive animals L II and treated L VII values at times T14 and T30;

At OFT-motility score: very significant increases at times T14 and T30, compared to the initial values T0 and compared to the control group L I at time T14; very significant increases at T14 and T30 compared to L VII treated animals;

In the Morris test for learning: very significant increases in values, compared to control group LI and compared to animals treated L VII at times T14 and T30; significant decreases in values at T14 and T30 compared to untreated animals L II;

In the Morris test for learning control: significant decreases in values compared to control values LI, compared to untreated depressive animals L II and treated L VII.

6.4.Conclusions

1. QUE + AGO treatment and supplementation with AGPN-Omega 3 cause depressed animals to decrease their sensitivity, increase their spontaneous motility, their ability to learn and control.

2. ARI + AGO treatment and supplementation with AGPN-Omega 3 cause depressed animals to decrease emotionality, increase spontaneous motility and the ability to learn and control.

3. Co-treatment with QUE + ESC and supplementation with AGPN-Omega 3 causes depressed animals to decrease their emotion, increase their spontaneous motility, their ability to learn and control.

4. Co-treatment with ARI + ESC and supplementation with AGPN-Omega 3 cause depressed animals to decrease emotionality, increase spontaneous motility and the ability to learn and control.

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