Experimental contributions in the pharmacotherapy of affective disorders in elderly

SUMMARY OF THE PhD THESIS

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INTRODUCTION

Depression or depressive episode is an pathological affective disorder, characterized by the presence of various emotional, physical, behavioral and cognitive symptoms, with manifestations varying in duration of progressive towards worsening, which lead, in time, to important deterioration of person current activities (domestic, social, professional), impairing his social and family relations (25,26). In depression, significant changes of the affective behavior and mood occur, with the predominance of a state of sadness, deep suffering and a slowdown of psychomotor activity.

Nowadays all over the world, life expectancy is growing, around 10% of the general population being persons aged over 65, which is passed on, to the increase of neurodegenerative diseases and also of affective disorders (22). This stage of life is associated with significant changes in the way that a person perceives himself and the world around, modifications manifested on all levels: biological, familial, professional, economical and social (44).

As the specific manifestations of depression in elderly, are known: the decrease of attention and concentration, lack of interest in others, memory deficits. These, are more pronounced while the person has various pathological states, sensory deficits and cognitive functions impairments (25,26).

The treatment of affective disorders is complex, associating pharmacotherapy with psychotherapy. The pharmacodynamic effects of antidepressants are obtained after a period of time, ranging between 2 and 4 weeks, period in which the psychotherapy proves its beneficial effects. It is well known that, in many cases, patients drop rapidly the medication, situations in which psychotherapy is particularly valuable, because it increases the patient’s compliance to treatment, due to the consolidation of trust in the therapeutic relationship.

There is a wide range of antidepressant drugs from different classes, with various mechanisms of action, showing indications in certain affective disorders, but also a lot of side effects, and the possibility of interactions with associated medication. In choosing the appropriate
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antidepressant, should be balanced, on the one hand its effectiveness in that disorder, and, on the other, the adverse effects that may occur (being mild, moderate, severe, temporary or lasting). Apart from their particular adverse effects, all antidepressants have been shown to increase the risk of suicide, especially at the beginning of the cure. That is why the patient must be supervised and supported by family.

JUSTIFICATION FOR CHOOSING THE THEME

Literature data shows that, in the therapy, antidepressants may have different effects in affective disorders, in many cases of geriatric depression, requiring judiciously choosing the optimal class of antidepressants.

In establishing the therapeutic scheme, with efficiency in the treatment of depression in elderly, should be carefully considered the risk-benefit ratio of each class of antidepressant used, taking into consideration the associated pathology (cardiovascular, hepatic, renal) of this particular category of patients and the medication that they follows.

In addition, it is extremely helpful to understand how different antidepressants affect the behavior and the cognitive functions of this specific age group, which presents a series of disturbances arising as a consequence of aging physiological process.

In this context, the choosing of this PhD thesis theme is justified, aiming to evaluate the effects of antidepressants, alone or in combination with magnesium in old animals.

The experimental studies of the thesis, consists of the investigation of some antidepressants influence on spontaneous motor behavior and cognitive functions in old laboratory animal.

Because many of antidepressants are currently indicated in the treatment scheme of elderly patients with affective disorders, it was considered useful, the idea of researching the influence exerted by some antidepressants with different mechanisms of action, alone or in association with magnesium, on different standardized behavioral models in old animals.
There were studied the effects that antidepressants: sertraline, paroxetine, reboxetine and venlafaxine, alone or in combination with magnesium chloride, produce on normal behavior in young and old laboratory animal.

In addition, it was carried out the assessing of the effects of antidepressants administration, in monotherapy or associated with magnesium (bivalent cation involved in numerous physiological processes in the body), on cognitive functions in young and old white Wistar rats.

The use of some internationally recognized experimental models for the study of behavior, motor activity and cognitive functions, offered the possibility of complex experimental researches, to evaluate the effects of these antidepressants in old animals.

Investigation of the interference produced by these antidepressants on cognitive functions, behavior and spontaneous motor activity, could result in obtaining new data regarding the pathophysiologic mechanisms of depression, but also providing useful information about pharmacotherapeutic possibilities of these drugs, in the treatment of various affective disorders in elderly.

Performing of these experimental researches on the laboratory animals, involved a teamwork and interdisciplinary collaboration, to achieve proposed goals.

**STATE OF KNOWLEDGE**

In the general part of the thesis are presented theoretical data regarding depression, detailing the elements related to: the history, classification, the epidemiology. There are highlighted particular aspects of depression in elderly, etiology, types, clinical manifestations, evolution and the pharmacotherapeutic management.

There are also described the main classes of antidepressants used to treat depression, by insisting on their pharmacokinetic, pharmacodynamic and clinical pharmacology particularities.

The PhD thesis has a number of 141 pages (from which 34 pages represent the state of knowledge and 86 pages constitute the own contributions) and includes a total of 94 tables and 55 figures. The
bibliography contains 370 references with Romanian and foreign authors. At the end of the paper is found the personal list with the articles published in ISI Web of Knowledge and international databases recognized journals.

PERSONAL CONTRIBUTIONS

The objectives of the study:

- experimental researches on the effects of some antidepressants (sertraline, paroxetine, reboxetine, venlafaxine), alone or in combination with magnesium chloride on spontaneous motor activity and behavior in young and old rats.
- experimental researches on the effects of some antidepressants (sertraline, paroxetine, reboxetine, venlafaxine), alone or in combination with magnesium chloride on the spatial memory in old rats.

Material and method:

**Substances:**

In order to achieve the objectives of the study, sertraline, paroxetine, reboxetine, venlafaxine, saline solution (Sigma-Aldrich Co., Germany) were administered in rats. Sertraline and paroxetine were dissolved in DMSO (dimethyl sulfoxide); reboxetine and venlafaxine in distilled water; the solutions being prepared immediately before the administration.

**Laboratory animals:**

White Wistar old rats (15-18 months), with an average weight between 300-350 g and uniform repartition by gender, from the Biobase University of Medicine and Pharmacy "Grigore T. Popa" - Iasi were used in the experiment. As the positive control animals, were considered the similar groups of white Wistar young rats (6-8 months), weighing 200-250g, which received the same doses of the substances, according to an identical protocol.

The experiments were performed using two sets of six groups of seven old rats (15-18 months) each, which received the substances orally (using an esogastric device) during 1 month as follows:
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Set I – old rats:
- **Group I.1-v. (M-v):** saline solution 0,5ml/100g weight – control;
- **Group I.2-v. (Mg-v):** magnesium chloride 1 mmol/kbw;
- **Group I.3-v. (SRT-v):** sertraline 3 mg/kbw;
- **Group I.4-v. (PRX-v):** paroxetine 5 mg/kbw;
- **Group I.5-v. (RBX-v):** reboxetine 5 mg/kbw;
- **Group I.6-v. (VLX-v):** venlafaxine 8 mg/kbw.

Set II – old rats:
- **Group II.1-v. (M-v):** saline solution 0,5ml/100g weight;
- **Group II.2-v. (Mg-v):** magnesium chloride 1 mmol/kbw;
- **Group II.3-v (SRT+Mg-v):** sertraline 3mg/kg+MgCl2 1mmol/kg;
- **Group II.4-v. (PRX+Mg-v):** paroxetine 5mg/kg+MgCl2 1mmol/kg;
- **Group II.5-v. (RBX+Mg-v):** reboxetine 5mg/kg+MgCl2 1mmol/kg;
- **Group II.6-v. (VLX+Mg-v):** venlafaxine 8mg/kg+MgCl2 1mmol/kg.

As the positive control animals were used the identical groups of young rats (6-8 months) which received the substances orally, during 1 month:

Set I – young rats:
- **Group I.1-t. (M-t):** saline solution 0,5ml/100g weight – control;
- **Group I.2-t. (Mg-t):** magnesium chloride 1 mmol/kbw;
- **Group I.3-t. (SRT-t):** sertraline 3 mg/kbw;
- **Group I.4-t. (PRX-t):** paroxetine 5 mg/kbw;
- **Group I.5-t. (RBX-t):** reboxetine 5 mg/kbw;
- **Group I.6-t. (VLX-t):** venlafaxine 8 mg/kbw.

Set II – young rats:
- **Group II.1-t. (M-t):** saline solution 0,5ml/100g weight;
- **Group II.2-t. (Mg-t):** magnesium chloride 1 mmol/kbw;
- **Group II.3-t (SRT+Mg-t):** sertraline 3mg/kg+MgCl2 1mmol/kg;
- **Group II.4-t (PRX+Mg-t):** paroxetine 5mg/kg+MgCl2 1mmol/kg;
- **Group II.5-t (RBX+Mg-t):** reboxetine 5mg/kg+MgCl2 1mmol/kg;
- **Group II.6-t (VLX+Mg-t):** venlafaxine 8mg/kg+MgCl2 1mmol/kg.

The evaluation of spontaneous behavior after the antidepressants administration was performed using the Actimeter test in rats, during experimental sessions of 20 minutes.
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The assessing of the influence exerted by the antidepressants on cognitive functions was conducted using the Y-maze test in rats, during experimental sessions of 8 minutes.

Fig. 1. Actimeter device

Fig. 2. Y-maze device scheme

Spontaneous alternation% = \[\frac{\text{alternations no.}}{\text{no. possible spontaneous alternations}}\] x 100, where: an alternation is defined as consecutive entry of the animal in three different arms of the device.

\text{No. possible spontaneous alternation.} = \text{total no. visited arms} - 2.

The experiments were conducted in compliance with the recommendations of the Ethics Committee of the "Grigore T. Popa" University - Iasi, in strict accordance with international ethical regulations regarding the handling of laboratory animals.

The results were expressed as mean values ± standard error of the mean (SEM) and statistically analyzed using SPSS program, version 13.0 for Windows and ANOVA unifactorial method.
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RESULTS

Actimeter Test

- reboxetine reduced the number of total and vertical movements in young rats, statistically significant (p < 0.05) compared to control in Actimeter test.

![Graph showing effects of antidepressants on total and horizontal movements in young rats.](image1)

**Fig. 3.** The effects of antidepressants on total and horizontal movements in Actimeter test in young rats. Each point represents the mean ± standard error of mean (SEM). *p < 0.05, **p < 0.01 vs. control.

![Graph showing effects of antidepressants on vertical and stereotype movements in young rats.](image2)

**Fig. 4.** The effects of antidepressants on vertical and stereotype movements in Actimeter test in young rats. Each point represents the mean ± ESM. *p < 0.05, **p < 0.01 vs. control.

- the association of reboxetine with magnesium chloride accentuated the reduction of the total, horizontal and vertical movements number in young rats, statistically significant (p < 0.05) compared to control, in this experimental behavioural model.
- the effects of antidepressants on the reduction of spontaneous behavior in young rats were in descending order the following:

  \[
  \text{RBX+Mg-t} > \text{VLX+Mg-t} > \text{PRX+Mg-t} > \text{SRT+Mg-t}
  \]
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**Fig. 5.** The effects of antidepressants associated with magnesium on the total and horizontal movements in Actimeter test in young rats. Each point represents the mean ± ESM. *p < 0.05, **p < 0.01 vs. control.

**Fig. 6.** The effects of antidepressants associated with magnesium on vertical and stereotype movements in Actimeter test in young rats. Each point represents the mean ± ESM. *p < 0.05, **p < 0.01 vs. control.

**Fig. 6.** The effects of antidepressants on the total and horizontal movements in Actimeter test in old rats. Each point represents the mean ± ESM. *p < 0.05, **p < 0.01 vs. control.

- the administration of the studied antidepressants decreased the total, horizontal and vertical movements number in old rats, statistically significant compared to control.
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**Fig. 8.** The effects of antidepressants on vertical and stereotype movements in Actimeter test in old rats. Each point represents the mean ± ESM. *p < 0.05, **p < 0.01 vs. control.

- the effects of the investigated substances on the decreasing of the total, horizontal and vertical movements number, in old rats were in descending order the following:
  
  VLX-v > Mg-v > RBX-v > SRT-v > PRX-v > M-v

**Fig. 9.** The effects of antidepressants associated with the magnesium on the total and horizontal movements in Actimeter test in old rats. Each point represents the mean ± ESM. *p < 0.05, **p < 0.01 vs. control.

**Fig. 10.** The effects of antidepressants associated with magnesium on vertical and stereotype movements in Actimeter test in old rats. Each point represents the mean ± ESM. *p < 0.05, **p < 0.01 vs. control.
the association of magnesium chloride to the studied antidepressants potentiated the reduction of the total, horizontal and vertical movements in old rats, statistically significant compared to control.

**Y-maze Test**

Fig. 11. Y - maze test - the effects of antidepressants on the total number of arms visited and the percentage of time spent in arms in young rats. Each point represents the mean ± ESM. *p < 0.05. **P < 0.01 vs. control.

- the effects of tested substances on the decrease of total arms visited number, were descending order the following:
  - Mg-t > RBX-t > VLX-t > PRX-t > SRT-t > M-t
  - VLX+Mg-t > RBX+Mg-t > PRX+Mg-t > SRT+Mg-t

Fig. 12. Y - maze test – the effects of antidepressants associated with magnesium on the total number of arms visited and the percentage of time spent in arms in young rats. Each point represents the mean ± ESM. *P < 0.05. **P < 0.01 vs. control.
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- the effects of studied substances on the increase of percentage of time spent in arms were in descending order the following:
  \[
  \text{Mg-t > RBX-t > VLX-t > PRX-t > M-t > SRT-t} \\
  \text{VLX+Mg-t > RBX+Mg-t > PRX+Mg-t > SRT+Mg-t}
  \]

![Fig. 14. Y-maze test - the effects of antidepressants on the number of alternations and the spontaneous alternation percentage in young rats. Each point represents the mean ± ESM. *P < 0.05. **P < 0.01 vs. control.]

- the effects of tested substances on the increase of alternations number were in descending order the following:
  \[
  \text{Mg-t > RBX-t > VLX-t > PRX-t > SRT-t > M-t} \\
  \text{VLX+Mg-t = RBX+Mg-t} = \text{PRX+Mg-t > SRT+Mg-t}
  \]

![Fig. 13. Y-maze test - the effects of antidepressants associated with magnesium on the number of alternations and the spontaneous alternation percentage in young rats. Each point represents the mean ± ESM. *P < 0.05. **P < 0.01 vs. control.]

- the effects of the studied substances on the increase of spontaneous alternation percentage, were in descending order the following:
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Mg-t > RBX-t > VLX-t > PRX-t > SRT-t > M-t
VLX+Mg-t > RBX+Mg-t > PRX+Mg-t > SRT+Mg-t

Fig. 15. Y-maze test - the effects of antidepressants on the total number of arms visited and the percentage of time spent in arms, in old rats. Each point represents the mean ± ESM. *P < 0.05. **P < 0.01 vs. control.

- the effects of the tested substances on the reduction of the number of entries into the arms of the device, were in descending order the following:

Mg-v > RBX-v > VLX-v > PRX-v > M-v > SRT-v
VLX+Mg-v > RBX+Mg-v > PRX+Mg-v > SRT+Mg-v

Fig. 16. Y-maze test - the effects of antidepressants on the number of alternations and the spontaneous alternation percentage in old rats. Each point represents the mean ± ESM. *P < 0.05. **P < 0.01 vs. control.

- the effects of the studied substances on the increase of percentage of time spent in arms, were in descending order the following:

Mg-v > RBX-v > SRT-v > VLX-v > M-v > PRX-v
VLX+Mg-v > RBX+Mg-v > PRX+Mg-v > SRT+Mg-v
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**Fig. 17.** Y-maze test - the effects of antidepressants associated with magnesium on the total number of arms visited and the percentage of time spent in arms in old rats. Each point represents the mean ± ESM.

*P < 0.05. **P < 0.01 vs. control.

- the effects of tested substances on the increase of the alternations number, were in descending order the following:

  \[
  Mg-v > RBX-v > VLX-v > PRX-v > SRT-v > M-v \\
  VLX+Mg-v > RBX+Mg-v = PRX+Mg-v > SRT+Mg-v
  \]

**Fig. 18.** Y-maze test - the effects of antidepressants associated with magnesium on the number of alternations and the spontaneous alternation percentage in old rats. Each point represents the mean ± ESM. *P < 0.05. **P < 0.01 vs. control.

- the effects of the studied substances on the increase of spontaneous alternation percentage, were in descending order the following:

  \[
  Mg-v > RBX-v > VLX-v > PRX-v > SRT-v > M-v \\
  VLX+Mg-v > RBX+Mg-v > PRX+Mg-v > SRT+Mg-v
  \]
CONCLUSIONS

- from the four antidepressants used in the experiment, reboxetine showed the most intense effects of reducing the spontaneous behavior and locomotor activity in Actimeter test, in young rats, and, respectively, venlafaxine in old rats;
- paroxetine showed the weakest effect of decreasing the spontaneous locomotor activity in this behavioral test, in both young and old rats.
- the association of magnesium chloride with venlafaxine, reboxetine, sertraline, respectively paroxetine in old rats, emphasized further reduction of spontaneous behavior in Actimeter test, actions that can be correlated, to some extent, with the sedative effect manifested in humans;
- the chronic treatment with reboxetine, venlafaxine and paroxetine produced the optimization of the animals cognitive functions in Y - maze test; reboxetine showing the most pronounced effects in the experiment;
- the administrition of sertraline during one month, did not exhibit significant influence on the short-term memory in young nor the old rats, in this behavioral model;
- the combination of magnesium chloride with the studied antidepressants (sertraline, paroxetine, reboxetine, venlafaxine) potentiated the facilitation of the spatial working memory, in both young and old rats in Y - maze test.

ASPECTS OF ORIGINALITY AND THE OUTLOOK OF PhD THESIS

Among the PhD thesis aspects of originality, are mentioned:
- providing a theoretical synthesis of the literature data regarding the classification, mechanisms of action and the pharmacodynamic effects of antidepressant medication;
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- presentation of pharmacokinetic elements of different classes of antidepressants, highlighting the aspects of their administration in elderly patient, which presents some particularities (related to the physiological process of aging, the associated pathological conditions and the medication received, especially the chronic one), which, in varying degrees, affect the absorption, transport, distribution, metabolism and elimination of these drugs from the body;
- highlighting the types of antidepressants that could be indicated in elderly persons with affective disorders, and presenting the risk / benefit and cost / efficacy ratios, for this category of patients;
- experimental research on the effects exerted by few antidepressants (sertraline, paroxetine, reboxetine, venlafaxine), alone or in association with magnesium, on the spontaneous behavior and motor activity in Actimeter test in the laboratory animal;
- experimental investigation on the effects performed by some antidepressants (sertraline, paroxetine, reboxetine, venlafaxine), alone, or in combination with magnesium, on spatial short-term memory in Y - maze test, in the laboratory animal;
- it was achieved a ranking of the intensity of pharmacodynamic effects produced by the tested antidepressants (sertraline, paroxetine, reboxetine, venlafaxine), alone or in association with magnesium, on the spontaneous behavior and the cognitive functions in these internationally recognized behavioral tests in rat.

It can be considered that the PhD thesis opens important perspectives for both fundamental medicine - by revealing the effects of some antidepressants (sertraline, paroxetine, reboxetine, venlafaxine) alone or in combination with magnesium, on the spontaneous behavior and cognitive functions in laboratory animals; and clinical practice - by highlighting the pharmacokinetic and pharmacodynamic characteristics of antidepressant medication, valuable elements for the specialist and family doctor, for selectioning and differentiated prescribing of the antidepressant therapy, in elderly patients with affective disorders.
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The obtained results by both performed theoretical metaanalysis and conducted experimental studies, represent a starting point for further researches, on the effects of antidepressants in elderly animal, in order to identify possible pharmacodynamic effects of these drugs, and to reveal the advantages offered by their association with other divalent cations (for example zinc).

The table of content included in this summary, comply with appropriate pagination existing in the thesis. The figures were renumbered for this material. The references presented in this text are identical to those in the PhD thesis.

SELECTIVE REFERENCES


**ANNEX. THE LIST OF PERSONAL PUBLISHED PAPERS**

**Papers in extenso**

