Experimental research on the action of some drugs in metabolic syndrome induced by antipsychotics in animals

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Introduction

Schizophrenia is a psychiatric syndrome that affects about 1% of the world’s population [1].

The age of onset of this condition has a similar distribution regardless of the diagnostic criteria, the highest rate being in the age group 16-25 years, followed by the age group 46-55 years and then over 65 years. The ratio between male and female is 1.56:1 in the age group 16-25 years, reaching unity around the age of 30 and decreasing to 0.38:1 in the 66-75 age group. [2,3]

To these worrying figures we can add the fact that the life expectancy of people with schizophrenia is 20% lower due to the disease itself, as well as due the high frequency of suicides and is 60% lower as a result of physical health problems.

Thus, prevention is difficult and therefore the onset and evolution of the disease is inevitable, researchers are trying to understand what is happening at the genetic and neurological level to develop appropriate therapies.

Today, all guidelines, recommendations and rules of assistance recommend as a first-line treatment of schizophrenia the atypical antipsychotic. The exception is clozapine, which, because of the risk of agranulocytosis / granulocytopenia, is a second-line antipsychotic, indicated only in cases resistant to treatment.

Initial enthusiasm for atypical antipsychotics, with a lower incidence of extrapyramidal symptoms, was tempered by their association with metabolic disorders. Numerous studies have shown a higher prevalence of metabolic syndrome in patients with schizophrenia compared to the general population.

Weight gain is the most recognized metabolic effect, although this varies significantly among atypical antipsychotics: clozapine and olanzapine have the highest risk, quetiapine and risperidone a moderate risk, aripiprazole, amisulpride and ziprasidone the lowest risk, with a negative impact on adherence to treatment and quality of life.

Insulin resistance has a prevalence of 30% higher, and diabetes is 1.5-2 times higher in the population receiving antipsychotics compared to the general population. Clozapine and olanzapine have the highest risk for hyperglycemia and diabetes, risperidone intermediate risk, and ziprasidone is the antipsychotic with negligible diabetes risk [4]

The PhD thesis takes into consideration the problem of metabolic side effects produced by one of the most atypical antipsychotic drugs, olanzapine, through experiment on animals.

At the same time, we have tried to evaluate by pharmacological methods, the effectiveness of some very recently cited and insufficiently studied drugs in the improvement of the metabolic syndrome generated by this psychiatric medication.

The PhD thesis is classically structured, with a general part describing the current state of knowledge in the field of pharmacology of schizophrenia, especially by presenting atypical antipsychotic drugs, metabolic syndrome, as an adverse effect of the group and the pharmacological intervention to improve it.

In the part of personal research are described the results obtained by in vivo experiment on animals with atypical antipsychotics, the evaluation of some parameters of the metabolic syndrome and the improvement of the parameters measured by metformin and melatonin treatment.
1. The stage of knowledge in the field of antipsychotic medication related to adverse effects and their prevention

Schizophrenia is a major psychiatric disorder, multisystemic, with a contoured neurobiological support characterized by affecting the whole personality.

The disease presents a great symptomatic heterogeneity, the main symptoms encountered in schizophrenia are grouped in positive symptoms (delirium, hallucinations), negative symptoms (affective flattening, apathy, hypobulia), cognitive impairment, depressive symptoms, behavioral manifestations such as psychomotor agitation or inhibition.

The most plausible mechanism of the pathogenesis of schizophrenia involves neurotransmitters - dopamine, serotonin, noradrenaline, histamine, glutamate, gamma-aminobutyric acid.

**Antipsychotics or neuroleptics** are drugs that electively influence *psychological processes* (cognitive, volitional, affective), with marked *antipsychotic effects*.

Within the antipsychotic effect, the drugs are classified into - antiproductive or reducing neuroleptics, antideficient neuroleptics, disinhibitors or incisors and polyvalent neuroleptics.

We have presented the classification of antipsychotics according to the basic chemical structure and the chronological order of their approval.

The mechanism of neuroleptics is probably due to the blocking of dopaminergic receptors in the brain, but without being able to explain how other neurotransmitters intervene.

Although all effective antipsychotics block D2 receptors, the degree of blocking compared to other actions on other receptors varies considerably.

Antipsychotics that bind more tightly than dopamine to D2 receptors have more pronounced extrapyramidal effects (examples: trifluperazine, chlorpromazine, haloperidol, flufenazine), and those that bind less than dopamine to D2 receptors have lower extrapyramidal effects (clozapine, sulphide, olanzapine, sertindol, quetiapine).

Because atypical antipsychotics act on a variety of receptors of dopaminergic, serotonergic, noradrenergic, histaminergic transmission, etc., we have included in a table the affinity degree of the different atypical antipsychotics after Miamoto et al, 2005. [5]

The pharmacological characteristics of the typical and atypical antipsychotics are exemplified in the table no. 2 with the individual description of the action mechanism and of the adverse effects. [6]

The pathophysiological mechanisms of weight gain following treatment with atypical antipsychotics by disturbing the hypothalamic control are presented according to current data.

Within the metabolic syndrome is presented the antipsychotic-induced diabetes, the characteristics of the metabolic syndrome, the involvement of adiponectin in the metabolic syndrome.

Although the number of animal studies used to decipher the mechanisms that produce metabolic syndrome is increasing rapidly, it is not possible to assert the existence of an animal model describing various disadvantages related to:

- controversy whether metabolic disorders are a direct effect of antipsychotics, or are pre-existing in patients with psychosis
  - very large gender difference in rats in weight gain
  - the difference in diet and the fact that antipsychotics have different pharmacokinetic properties in rats than humans.
  - different feeding period in rats eating in the dark and postprandial changes in glucose
- Antipsychotics side effects in animals such as sedation and muscle rigidity decrease activity and alter metabolism, influencing antipsychotic interactions on food intake, especially in short-term studies. [7]

- Age, because most studies have used adult animals as compared to the clinic where many patients begin treatment in childhood and adolescence, being more predisposed to weight gain.

The current models are not perfect, but they are extremely important in addressing the problems associated with atypical antipsychotics.

Pharmacological interventions that can limit or prevent the secondary metabolic effects of antipsychotic drugs have been studied and are still being studied.

In 32 studies, there were included 1482 subjects and there were tested 15 different drugs: amantadine, dextroamphetamine, d-fenfluramine, famotidine, fluoxetine, fluvoxamine, metformin, nizatidine, orlistat, phenylpropanolamine, reboxetine, rosiglitazone, sibutramine, metam + sibutramine compared to placebo, metformin had the highest weight loss (2.94kg), followed by d-fenfluramine (2.60kg), sibutramine (2.56kg), topiramate (1.90kg).

Weight loss remained significant upon initiation of metformin after weight gain, but was not initiated concomitantly with antipsychotics.

In total, 5 of the 15 psychopharmacological interventions aimed at improving weight gain induced by antipsychotics exceeded placebo. The results were the most significant for metformin, although they were modest and heterogeneous, with only one combined treatment study being available that was negative. [8]

Several studies claim that melatonin has improved metabolic syndrome. [9]

2. Experimental research on the action of some drugs in metabolic syndrome induced by antipsychotics in animals

In the second part, which represents 2/3 of the thesis, we have presented the personal experimental research on the action of some drugs in the metabolic syndrome induced by antipsychotics in animals.

2.2. Motivations for the research

Our aim was to investigate the action of olanzapine pamoate, an atypical antipsychotic in pharmaceutical depot form, in inducing some changes in metabolic homeostasis.

One of the mechanisms suggested to generate these adverse effects is a decrease in the plasma concentration of melatonin, a hormone of the pineal gland [10].

The decrease in plasma melatonin concentration is related to the metabolic syndrome on the one hand by altering the sleep-wake circadian rhythm (melatonin, a chronobiotic known), and on the other hand by diminishing direct activities such as antioxidant, neuroprotective and immunomodulatory action [11]. We have found it interesting to study the influence of melatonin administration on metabolic changes induced by olanzapine depot in rats.

Because changes in carbohydrate and lipid metabolism occur in chronic olanzapine administration, we have also studied the action of metformin on metabolic changes produced by olanzapine, an antidiabetic that increases tissue insulin sensitivity but also produces a moderate weight loss through a central mechanism. We have associated olanzapine, melatonin and metformin in the chronic experiment with antipsychotics to determine possible pharmacodynamic interactions.
2.3. Purpose and objectives of the research

The purpose of the study is to identify the occurrence of a possible metabolic syndrome after the treatment with one of the antipsychotics with the highest incidence in the production of the metabolic syndrome, namely Olanzapine, and to counteract these effects by co-administration of an anti-diabetic (Metformin) or a hormone secreted by the pineal gland with a role in regulating the circadian rhythm (Melatonin).

My research objectives aimed at:
- determination of blood antipsychotic concentration by HPLC method
- establishing the correlations between antipsychotic treatment and weight gain
- monitoring the amount of food and water consumed in the case of single antipsychotic treatment (olanzapine pamoate), as well as in the case of double (with melatonin or metformin) and triple combination
- investigation of thermogenesis in the case of single antipsychotic treatment, as well as in the case of double and triple association
- monitoring of metabolic parameters when administering olanzapine pamoate: glucose in acute and chronic experiments, cholesterol, triglycerides
- establishing the correlations between the treatment with the investigated antipsychotic and the growth of subcutaneous and visceral adipose tissue
- investigating the simultaneous effect of antipsychotic and metformin on the evolution of the weight curve and subcutaneous and visceral adipose tissue
- investigating the simultaneous effect of antipsychotic and metformin on levels of metabolic parameters (blood glucose in acute and chronic experiment, cholesterol, triglycerides)
- investigating the simultaneous effect of antipsychotic and melatonin on the level of metabolic parameters (blood glucose in acute and chronic experiment, cholesterol, triglycerides)
- investigating the simultaneous effect of antipsychotic and metformin on the evolution of the weight curve and subcutaneous and visceral adipose tissue
- investigating the simultaneous effect of antipsychotic, metformin and melatonin on metabolic parameters level (blood glucose in acute and chronic experiment, cholesterol, triglycerides)
- investigating the simultaneous effect of antipsychotic, metformin and melatonin on the evolution of the weight curve and subcutaneous and visceral adipose tissue
- comparison in the weight of the liver, kidney, heart, pancreas, at the end of the study after slaughtering the animals from the study groups and the histopathological analysis following the treatment with olanzapine and the combination with metformin, melatonin and the both of them
- histopathological analysis of vital organs (heart, liver, kidney, pancreas) and subcutaneous and visceral adipose tissue at the end of the study after animal sacrifice.

2.4. Materials and methods

There were used 35 female Wistar rats kept in optimal laboratory conditions, which were divided into 7 groups: one group for plasma concentration dosing by HPLC, one control group, one group treated with i.m. injected olanzapine pamoate at 14 days, a group treated with olanzapine pamoate i.m. at 14 days and melatonin daily by gavage, another group treated with olanzapine pamoate i.m. at 14 days and metformin daily by gavage and the last group treated with olanzapine pamoate i.m. at 14 days and melatonin + metformin daily by gavage. The duration of the research was of 8 weeks.
Working method throughout the experiment:

- The animals in group 1 were weighed weekly, in order for the medicine to be administered at the dose corresponding to the body weight of each animal. Following administration of Olanzapine pamoate i.m 100 mg / kg blood was collected 3 days in a row, then at one week and at two weeks post-administration. Blood was used to dose the blood concentration of olanzapine pamoate by HPLC method corresponding to the respective period.

- The animals from groups 2, 3, 4, 5 and 6 were weighed in the morning, between 9 and 10, every 3 days in the first 2 weeks and then once a week until the end of the experiment. A drop of blood was collected from the tail, daily during the first 4 days of the experiment and then weekly which was subjected to analysis at the GCT Multicare IN Analyzer. Corresponding to the days of administration of the antipsychotic, namely on days 1, 15, 29 and 43, a drop of blood was collected for acute blood glucose dosing, being collected before and at one hour after the administration of the antipsychotic. The body temperature was monitored in the morning, weekly, with the help of a multifunctional infrared thermometer A&D MEDICAL - UT-80. The quantity of food and water consumed in each group was monitored, animals were housed in cages of 6 animals, the quantity of food was weighed at the beginning of the week and at the end of the week, the water was placed in graded containers and so the daily consumption by group could be monitored. 24 hours after the last administration of the medicinal substances the animals were subjected to a general anesthesia procedure and sacrificed, collecting from each animal the liver, heart, pancreas, kidneys, visceral and subcutaneous adipose tissue. Biological materials were weighed and processed for permanent histological preparation.

The experiment was carried out in accordance with the rules of the Commission for Animal Welfare and with the approval of the Commission for Ethics and Professional and Scientific Deontology of the University of Medicine and Pharmacy Craiova.

2.5. Statistical analysis

Statistical analysis was performed using a dedicated program - IBM SPSS vers 23.

For the descriptive analysis of the groups, the average, the minimum and maximum value, the standard deviation were used.

For the data comparison, the Z score with 95% specificity threshold (p < 0.05) was used, and this was calculated by the following nonparametric tests: Mann-Whitney test and Wilkoxon test.

2.6 Results, discussions and partial conclusions

The chapter has a number of 12 sub-chapters in which the changes on the clinical, biochemical and histopathological parameters are discussed separately, discussed on the basis of the current data from the specialized literature, with the elaboration of partial conclusions for each sub-chapter.

The sub-chapter entitled "Determination of plasma olanzapine concentration using HPLC and its correlation with the administration period" aims to highlight the presence of olanzapine in plasma to show that the administration of olanzapine pamoate at 14 days i.m. is optimal.

In subchapter 2 "The evolution of the weight curve during the study under the action of olanzapine pamoate and the combination of olanzapine pamoate with melatonin
and metformin in rat" it is found that olanzapine pamoate produces a weight gain in the acute experiment (the first 4 weeks) but not in the chronic experiment (5-8 weeks), melatonin potentiates olanzapine pamoate-induced weight gain, and metformin antagonizes this effect.

In subchapter 3 "Analysis of food consumption during 8 weeks of study on group of rats treated with olanzapine pamoate and the combination of olanzapine pamoate with melatonin and metformin" it is found that the highest consumption of food was found in the group treated with olanzapine pamoate and the lowest in the group with olanzapine pamoate and metformin.

In subchapter 4 "Analysis of water consumption during 8 weeks of study on groups of rats treated with olanzapine pamoate and the combination of olanzapine pamoate with melatonin and metformin" it is shown that the groups with olanzapine pamoate and olanzapine pamoate + melatonin presents an increase in water consumption in the first part of the study, following a decrease in the second part of the study, and the groups with olanzapine pamoate + metformin and the one with the triple combination show a reversal of the ratio.

Another followed parameter was the temperature of the animals, given the rare cases of hypothermia in the literature, sometimes fatal to antipsychotics. In subchapter 5 "The evolution of the temperature curve during the study under the action of olanzapine pamoate and the combination of olanzapine pamoate with melatonin and metformin in rats" it is noted that olanzapine pamoate decreases the body temperature at the end of the study as compared to the control group. Melatonin and metformin partially antagonize the hypothermic effect of olanzapine pamoate.

In subchapter 6 "Changes in blood sugar one hour after i.m. injection of olanzapine pamoate at 2-week intervals by association with melatonin, metformin and melatonin + metformin p.o. daily "describes how olanzapine pamoate invariably produces an increase in blood sugar one hour after administration, and the action of reducing blood sugar one hour after injecting olanzapine pamoate increases in the order of melatonin <metformin <melatonin + metformin.

In subchapter 7 "Modifications of basal blood sugar during the experiment by i.m. injecting of olanzapine pamoate at 2-week intervals and its association with melatonin, metformin and melatonin + metformin p.o. daily" it is shown that the differences between the comparative blood glucose levels of each group paired with the control group or the group treated with olanzapine pamoate are mostly statistically insignificant during the study.

In subchapters 8 and 9, the parameters of lipid metabolism, cholesterol and triglycerides are analyzed, finding an insignificant variability of cholesterol, but an increase of serum triglycerides with olanzapine pamoate, increases maintained throughout the study at comparatively higher values than the control; melatonin association decreased triglyceride levels, as well as metformin and triple association decreased triglyceride levels in the final part of the study.

In subchapter 10 "Quantitative changes of adipose tissue to the combination of olanzapine pamoate melatonin and metformin" after slaughter of animals, at the end of the experiment, subcutaneous and visceral adipose tissue was collected and after weighing there was a quantitative increase of both tissues in olanzapine pamoate group with predominance of visceral adipose tissue. The groups treated with olanzapine and metformin and with olanzapine pamoate, melatonin and metformin have a very small amount of visceral adipose tissue.

In subchapter 11 "Comparison of viscera weight in the 4 groups of animals" the average differences in viscera weight in the study groups compared to the control or to the olanzapine-treated group are generally insignificant. In the group with olanzapine pamoate, average weights of the larger viscera were recorded, especially of the kidneys. The liver has a
higher weight in the group treated with olanzapine pamoate and melatonin and lower in the group treated with metformin. In the group with olanzapine pamoate with metformin the heart and kidneys have less weight, but with increasing weight of the pancreas.

In the last chapter "Histopathological analysis of the liver, heart, pancreas, kidneys, skeletal and visceral adipose tissue after treatment with depot olanzapine and the combination with metformin, melatonin and both" various lesions are discovered in the liver produced by olanzapine pamoate antagonist or more or less exacerbated by melatonin and metformin as it follows:

- passive congestion of the liver when administering olanzapine pamoate; the phenomenon being accentuated by the addition of melatonin and attenuated by the administration of metformin, maintaining the protective effect and the association with melatonin.
- many inflammatory cells surrounding the Kiernan space are described in the group treated with olanzapine pamoate, a phenomenon attenuated less by melatonin and more by metformin. The attenuation phenomenon is also maintained in combination but not to the same extent as the effect of metformin alone.
- a diffuse panlobular steatosis is described in the group treated with olanzapine pamoate, affecting the entire hepatic lobe; the protective effect of melatonin is uncertain, there was no significant improvement of olanzapine-induced hepatosteatosis. Metformin administration attenuates the onset of olanzapine pamoate-induced hepatosteatosis.

Olanzapine pamoate has produced significant renal damage, and melatonin and metformin have no protective effect, on the contrary, it causes more severe renal injury.

In adipose tissue after administration of olanzapine pamoate lipid vacuoles are surrounded by inflammatory cells; lipid vacuoles without inflammatory cells were recorded in combination with melatonin or metformin, with smaller lipid vacuoles at triple association.

Olanzapine pamoate causes lesions to the myocardium, describing the dilatation of the lymphatic vessels, being present an edema characteristic of a heart failure. The protective effect of melatonin is evident in the group treated with olanzapine pamoate + melatonin and histopathologically significant reduction of cardiac edema was observed. In the groups where metformin is associated, there is an obvious protective effect due to the complete lack of edema, without showing any cardiac pathological change.

No lesion to the pancreas is detected in any of the studied groups, no changes in the endocrine or exocrine component

3. Final conclusions

1. Using the HPLC dosing method, effective concentrations of olanzapine at plasma level are observed in the rat, which are maintained for 14 days.
2. Olanzapine pamoate causes weight gain in the acute experiment (first 4 weeks), but not in the chronic experiment (8 weeks).
3. Compared to the consumption of food and water that increases physiologically with the increase of age in the control group, in the case of olanzapine pamoate the consumption knows a constant increase only during the acute experiment stage, with stationary or decrease of the consumption during the chronic experiment stage.
4. The administration of Olanzapine pamoate invariably results in an increase in blood sugar one hour after administration, which is remitted until the next
day, without significant fluctuations in the plasma concentration of basal blood glucose until the next administration.

5. The control group and the group treated with olanzapine pamoate had a mean blood glucose at the end of the study lower than its initial value, below 90%, but statistically significant.

6. Olanzapine pamoate did not cause an increase in total serum cholesterol in the control group and did not increase total serum cholesterol at the end of the study.

7. Olanzapine pamoate caused increases in serum triglycerides, increases maintained throughout the study at comparably higher values than the control.

8. The amount of predominant visceral adipose tissue and subcutaneous adipose tissue increases in the olanzapine pamoate treated group compared to the control group.

9. The hypothermizing effect of olanzapine pamoate in rats is statistically significant from week 3 and the decrease in body temperature at the end of the study compared to the onset is 1.42%.

10. Compared to the control, the average weights of the viscera were statistically insignificant in the group treated with olanzapine pamoate, especially in the kidneys.

11. The weight gain deficit compared to the control at the end of the study is reduced from 8.40% in the olanzapine pamoate treated group to 4.53% in the olanzapine pamoate and melatonin treated group.

12. In the study groups the weekly consumption of food decreased at the end of the study in the order olanzapine pamoate > olanzapine pamoate + melatonin > olanzapine pamoate + melatonin and metformin > olanzapine pamoate + metformin.

13. The increase in water consumption is permanent from week 3 to week 8 in the group treated with olanzapine pamoate and melatonin + metformin, and from week 7 it exceeds the increase in consumption in the group treated with antipsychotic.

14. The action of reducing blood sugar to one hour after injection of olanzapine pamoate increases in the order of melatonin < metformin < melatonin + metformin.

15. The differences between the basal blood glucose levels compared in each group paired with the control group or the group treated with olanzapine pamoate are mostly statistically insignificant during the study.

16. The combination of olanzapine pamoate with melatonin, metformin or melatonin and metformin causes a reduction in total serum cholesterol relative to the control group, statistically insignificant, which is accentuated in the order olanzapine pamoate < olanzapine pamoate + melatonin < olanzapine pamoate + metformin < olanzapine pamoate + melatonin + metformin.

17. The percentage of increase or decrease of the average value of serum triglycerides in the study groups at the end of the experiment was as follows: the control group + 16.69%; the group treated with olanzapine pamoate + 21.28%; the group treated with olanzapine pamoate and metformin + 5.86%; the group treated with olanzapine pamoate and melatonin - 18.90%; the group treated with olanzapine pamoate and melatonin + metformin - 23.18%.

18. The percentage of subcutaneous adipose tissue from visceral adipose tissue decreases in the following order of groups: group treated with olanzapine pamoate (56.65%) > group treated with olanzapine pamoate + melatonin

19. The combination of olanzapine pamoate with melatonin, metformin or metformin and melatonin causes a reduction in total serum cholesterol relative to the control group, statistically insignificant, which is accentuated in the order olanzapine pamoate < olanzapine pamoate + melatonin < olanzapine pamoate + metformin < olanzapine pamoate + melatonin + metformin.
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(41.43%) > olanzapine pamoate + metformin (40.47%) > olanzapine pamoate + melatonin and metformin (33.52%), close to the ratio in the control group (32.31%).

19. Olanzapine pamoate causes hypoglycaemia. The difference between the average temperature values at the end of the study and its onset decreases in the order: olanzapine (1.42%) > olanzapine pamoate + metformin (1.08%) > olanzapine pamoate + melatonin (0.97%) > olanzapine pamoate + melatonin and metformin (0.78%) > control.

20. Passive congestion of the liver when administering olanzapine pamoate is accentuated by the addition of melatonin and attenuated by the administration of metformin, maintaining its protective effect in combination with melatonin.

21. In the group treated with olanzapine pamoate, many inflammatory cells surrounding the Kiernan space are described, phenomenon less attenuated by melatonin and more by metformin. The attenuation phenomenon is also maintained in combination but not to the same extent as the effect of metformin alone.

22. A diffuse panlobular steatosis is described in the group treated with olanzapine pamoate, affecting the entire hepatic lobe although in the experiment no hyperphagia and smaller centrolobular steatosis were reported, an aspect that is due to the hypoxia produced by dilatation of the centrolobular vein.

23. The protective effect of melatonin is uncertain, there was no significant improvement of olanzapine-induced hepatosteatosis, perhaps because it has a diet-independent appearance.

24. Metformin administration attenuates the onset of olanzapine pamoate-induced hepatosteatosis.

25. Olanzapine pamoate causes lesions in the myocardium, describing the dilatation of the lymphatic vessels, being present an edema characteristic of a heart failure.

26. The protective effect of melatonin at the level of the myocardium is present in the group treated with olanzapine pamoate + melatonin, showing a significant histopathological reduction of edema.

27. In the groups in which metformin is associated, there is an obvious protective effect due to the complete lack of edema, without highlighting a possible cardiac pathological change.

28. No histopathological changes of the pancreas appear in any of the studied groups, both in the endocrine and exocrine components.

29. In the group treated with olanzapine pamoate the visceral adipose tissue vacuoles are in a similar proportion to the skeletal one but in the visceral one they are surrounded by inflammatory cells.

30. In the group treated with olanzapine pamoate + melatonin, large lipid vacuoles are evident in both adipose tissues but a large vacuolization is prevalent in visceral adipose tissue.

31. In the group treated with olanzapine pamoate + metformin the visceral adipose tissue is slightly fibrous, being similar to the skeletal one, without signs of inflammation.

32. In the case of triple association, both visceral and skeletal adipose tissues have small lipid vacuoles.

33. Olanzapine pamoate caused remarkable changes in renal architecture, demonstrated by the expansion of capsular space and tubular degeneration.
34. The protective effect of melatonin and metformin is lacking, on the contrary the lesions are more obvious in the double combination and very pronounced in the triple combination.

35. Small groups of animals do not allow us to express categorically that the favorable actions found for the combination of olanzapine depot with melatonin and metformin can be used in therapeutic practice, although such statements are made in some publications.

36. In addition, the negative histological aspects at the renal level make us look at these associations with caution.

Selective Bibliography:


