

# Antidepressant effect of the interaction of fluoxetine with granisetron

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**Abstract.** Selective serotonin reuptake inhibitors (SSRIs) may produce digestive side effects such as nausea and vomiting, diarrhoea and decreased appetite. These side effects are determined by the increase in serotonin availability at 5-HT<sub>3</sub> receptors. Granisetron, a serotonin 5-HT<sub>3</sub> receptor antagonist, is expected to antagonize the digestive adverse effects of serotonin reuptake inhibitors, but the question is to what extent granisetron influences the antidepressant effect of these substances. The aim of this study was to determine the dose of fluoxetine that has an antidepressant effect in the Porsolt test, and the interaction between fluoxetine and granisetron with respect to the antidepressant effect in this test. In experiment 1, fluoxetine was antidepressant only at 20 mg/kg body weight (bw). In experiment 2, granisetron 1 mg/kg bw had a statistically significant antidepressant effect vs. control. Fluoxetine 20 mg/kg bw associated with a small dose of granisetron (0.1 mg/kg bw) produced a significant antidepressant effect vs. control. This shows that low doses of granisetron associated to fluoxetine might produce a significant antidepressant effect, suggesting a potentiation between these two drugs used in sub-effective antidepressant doses. In conclusion, in our experimental conditions, we can assume that granisetron in low doses could be used to combat intestinal transit disorders produced by SSRI antidepressants. These low doses are preferred, because they increase the antidepressant effect of these SSRIs.

## Introduction

Some antidepressants and some antipsychotics act as antagonists on the 5-HT<sub>3</sub> receptor. This receptor has binding sites for antidepressant and antipsychotic drugs, so that the 5-HT<sub>3</sub> receptor is a therapeutic target in the treatment of depression and psychosis as an additional mechanism to the already known classical ones (1).

5-HT<sub>3</sub> receptors belong to the superfamily of receptors coupled to ion channels, structurally similar to GABA A receptors, nicotinic receptors and glycine receptors. Localized in central and peripheral neurons, they generate rapid depolarization resulting from the opening of cationic channels (Na<sup>+</sup>, K<sup>+</sup> and Ca<sup>2+</sup> ionic currents). Structurally, it is a five-unit pentamer that surrounds a central channel. There are numerous 5HT<sub>3</sub> receptor subfamilies (2).

There are studies that have shown that tricyclic antidepressants such as imipramine, desipramine, doxepin, monoamine oxidase inhibitors (MAOIs) such as phenelzine (3), along with SSRIs such as fluoxetine uncompetitively inhibit 5-HT<sub>3</sub> transreceptor currents (4). Also, endogenous substances such as sphingolipids and cholesterol regulate channel opening of 5-HT<sub>3</sub> receptors (5,6).

Selective serotonin reuptake inhibitors (SSRIs) may produce digestive side effects such as nausea and vomiting, diarrhoea and decreased appetite. These side effects are determined by the increase in serotonin availability at 5-HT<sub>3</sub> receptors (7).

Granisetron, a serotonin 5-HT<sub>3</sub> receptor antagonist, is expected to antagonize the digestive adverse effects of serotonin reuptake inhibitors. However, the question is to what extent granisetron influences the antidepressant effect of these substances.

The aim of the present study was to determine the dose of fluoxetine that has an antidepressant effect in the Porsolt test (classical variant of the forced swimming test) and the interaction between fluoxetine and granisetron with respect to the antidepressant effect in the Porsolt test.

## Materials and methods

NMRI Swiss albino strain mice, 25-30 g, from the 'Carol Davila' University hatchery were used. Animals were brought

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*Abbreviations:* 5HT, serotonin; MAOIs, monoamine oxidase inhibitors; SSRIs, selective serotonin reuptake inhibitors

*Key words:* serotonin, fluoxetine, granisetron, antidepressant

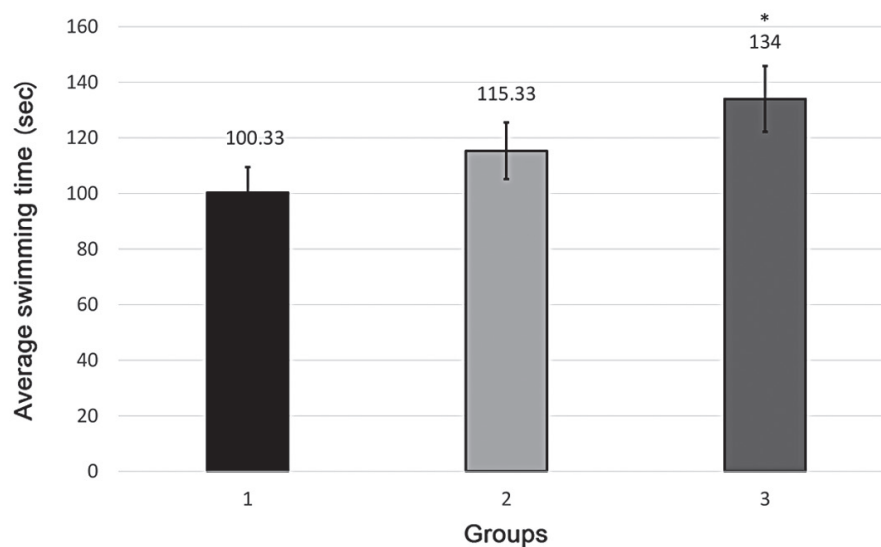


Figure 1. Length of the columns represent the average of motility times (sec) for each group. Group 1, control:  $100.33 \pm 9.1$ ; group 2, fluoxetine 10 mg/kg bw:  $115.33 \pm 10.2$ ; group 3, fluoxetine 20 mg/kg bw:  $134 \pm 11.83$ , \* $P < 0.05$ , statistically significant, as an expression of an antidepressant effect in forced swimming test (Porsolt).

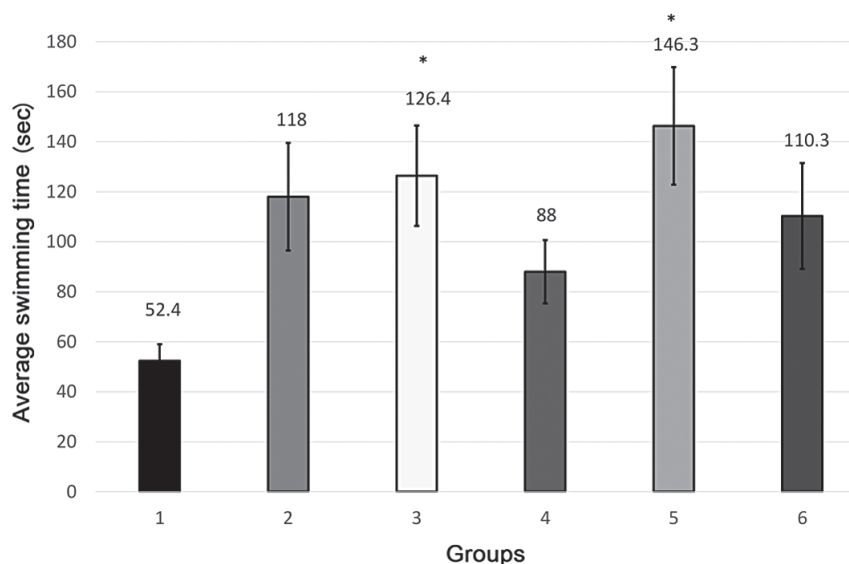


Figure 2. Length of the columns represent the average of motility times (sec) for each group. Group 1, control:  $52.4 \pm 6.64$ ; group 2, granisetron 0.1 mg/kg bw:  $118 \pm 21.52$ ; group 3, granisetron 1 mg/kg bw:  $126.4 \pm 20.09$ ; group 4, fluoxetine 20 mg/kg bw:  $88 \pm 12.66$ ; group 5, fluoxetine 20 mg/kg bw + granisetron 0.1 mg/kg bw:  $146.3 \pm 23.48$ ; group 6, fluoxetine 20 mg/kg bw + granisetron 1 mg/kg bw:  $110.3 \pm 21.38$  in forced swimming test (Porsolt). \* $P < 0.05$  vs. control group.

Table I. P-values of the tests of significance in experiment 1.

Experiment 1	Group 1	Group 2	Group 3
Group 1	-	0.549	<b>0.049</b>
Group 2	0.549	-	0.398
Group 3	<b>0.049</b>	0.398	-

Statistically significant values were figured in bold numbers.

to the accommodation at least 3 days before the experiments and were kept under standard laboratory conditions, housed in plexiglass cages with sawdust, 12 mice per cage, and were

supplied with granulated food and water *ad libitum*, at an ambient temperature of 21-24°C and a relative humidity of 45-60%, in a normal dark-light cycle (07:00-19:00 h). The number of animals per group was set at 15 (experiment 1) and 10 (experiment 2). The experiments were approved by the Institutional Ethics Committee of Faculty of Medicine, UMF Carol Davila (Bucharest, Romania).

Substances used were: granisetron solution 1 mg/ml (Granisetron Kabi 1 mg/ml), fluoxetine powder (Medochemie, Cyprus, an internal standard) administered intraperitoneally in concentrations calculated to administer 5 ml/kg body weight.

Experiment 1 used 3 groups: The control group, saline; group 1, fluoxetine 10 mg/kg; group 2, fluoxetine 20 mg/kg, all administered intraperitoneally 30 min before testing.

Table II. P-values of the tests of significance in experiment 2.

Experiment 2	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Group 1	-	0.107	<b>0.048</b>	0.710	<b>0.005</b>	0.203
Group 2	0.107	-	0.999	0.833	0.864	1.000
Group 3	<b>0.048</b>	0.999	-	0.640	0.967	0.987
Group 4	0.710	0.833	0.640	-	0.197	0.946
Group 5	<b>0.005</b>	0.864	0.967	0.197	-	0.700
Group 6	0.203	1.000	0.987	0.946	0.700	-

Statistically significant values were figured in bold numbers.

In experiment 2, 6 groups were used: Control group, saline; group 2, granisetron 0.1 mg/kg; group 3, granisetron 1 mg/kg; **group 4, fluoxetine 20 mg/kg; group 5, granisetron 0.1 mg/kg + fluoxetine 20 mg/kg; group 6, granisetron 1 mg/kg + fluoxetine 20 mg/kg**, administered intraperitoneally 30 min before testing.

Berzelius glasses 18/10 cm height/diameter filled with water at a height of 12 cm and temperature of 28°C and video recording system were used.

The tests were conducted in natural light between 8.30 and 16.30. The parameter used for processing was the swimming time in the last 4 min of a 6-min swimming session. The reading of the results was blind (mice were divided into three Berzelius glasses simultaneously, varying the position of introduction into glass 1, 2 or 3 of each group of animals), according to a test protocol. Swimming was defined as active horizontal or vertical movements at the surface of the water.

Antidepressant drugs increase animal mobility during the last 4 min of the test. It is considered that the duration of the mobility time in these last 4 min is directly proportional with the intensity of the antidepressant effect of a substance.

*Statistical analysis.* Microsoft Excel and SPSS 25 were used for statistical analysis. For each group means and standard errors were calculated. ANOVA and post-hoc test Tukey were used because the groups had homogeneous variance (Levene statistic test >0.05). P<0.05 was considered as statistically significant.

## Results and Discussion

Only the 20 mg/kg dose of fluoxetine significantly increased the mobility time (Fig. 1; Table I). Increase in the mobility time in Porsolt test is considered throughout the literature as an expression of an antidepressant effect. Since only this dose of fluoxetine had statistically significant antidepressant effect vs. control, this dose was used in experiment 2.

In experiment 2, only group 3, granisetron 1 mg/kg bw and group 5 fluoxetine 20 mg/kg bw + granisetron 0.1 mg/kg bw significantly increased the mobility time of the animals in the Porsolt test, which is consistent with a statistically significant antidepressant effect (Fig. 2; Table II).

Granisetron at the high dose (1 mg/kg bw) had a statistically significant antidepressant effect vs. control. Fluoxetine 20 mg/kg bw had no statistically significant effect in this

test, result that may be considered unexpected taking into account the significance obtained at the same dose in the first experiment.

Fluoxetine 20 mg/kg bw associated with a small dose of granisetron (0.1 mg/kg bw) produced a significant antidepressant effect vs. control. This shows that low doses of granisetron associated with fluoxetine might produce a significant antidepressant effect, suggesting a potentiation between these two drugs used in sub-effective antidepressant doses.

Fluoxetine 20 mg/kg bw associated with a high dose of 1 mg/kg bw of granisetron had no antidepressant effect vs. control.

Based on the above aspects and the data obtained, we state that in our experimental conditions, it cannot be asserted that the association of granisetron to fluoxetine has a potential risk of diminishing the antidepressant effect of fluoxetine. Moreover, in our experimental conditions, granisetron seems to have an antidepressant effect *per se*.

At low doses, granisetron seems to potentiate the effect of fluoxetine, but this increase disappears at high doses of granisetron. Based on the results obtained in this study, we cannot reliably consider the mechanism of interactions between fluoxetine and granisetron relating to the antidepressant effect.

In literature, one can find that stimulation of 5-HT<sub>3</sub> receptors activates the nitric oxide-cyclic guanosine monophosphate pathway, which is involved in regulating behaviour and emotional functions (8).

A research study on an antidepressant effect of a 5HT<sub>3</sub> receptor antagonist N-(benzo[d]thiazol-2-yl)-3-methoxyquinoxalin-2-carboxamide (6z) showed improvements of swimming in forced swimming test at psychomotor non-stimulating doses (9). Besides the above results, ondansetron, tropisetron, code-named substance QCF-3 ((4-benzylpiperazin-1-yl) (quinoxalin-2-yl) methanone), code-named substance MDL 72222 (1 alpha H, 3 alpha, 5 alpha H-tropan-3-yl-3,5-dichlorobenzoate) and 2-(4-methyl piperazin-1-yl)-1,8-naphthyridine-3-carbonitrile proved antidepressant effects in some paradigms of antidepressant activity (10-14).

Corroborating all the experimental results obtained in this investigation, we can say that since SSRI antidepressants increase serotonin availability in serotonin synapses, granisetron may antagonize the digestive side effects of these antidepressants. Moreover, granisetron seems to have an antidepressant effect *per se*. At low doses, granisetron appears to increase the antidepressant effect of selective

serotonin reuptake inhibitors, an effect that disappears with high doses.

In conclusion, based on the data obtained in our experimental conditions, we can assume that granisetron in low doses could be used to combat intestinal transit disorders produced by SSRI antidepressants. These low doses are preferred, because based on our experimental data they increase the antidepressant effect of these SSRIs.

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### Availability of data and materials

Data could be consulted upon request.

### Authors' contributions

MC made substantial contributions to the acquisition, analysis, and interpretation of data for the study and participated in the drafting of the study. HP made substantial contributions to the design of the study and participated in the drafting of the study and in revising it critically for important intellectual content. OAC made substantial contributions to the analysis and interpretation of data for the study and participated in the drafting of the study and in revising it critically for important intellectual content. LC made substantial contributions to the analysis and interpretation of data for the study and participated in the drafting of the study. IF made substantial contributions to the conception and design of the study and participated in revising it critically for important intellectual content. All authors gave their final approval of the version to be published and agreed to be accountable for all aspects of the study in ensuring that questions related to the accuracy or integrity of any part of the study are appropriately investigated and resolved.

### Ethics approval and consent to participate

The experiments were approved by the Institutional Ethics Committee of Faculty of Medicine, UMF Carol Davila (Bucharest, Romania).

### Patient consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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