https://journal.utripoli.edu.ly/index.php/Alqalam/index eISSN 2707-7179

Original article

The Dark Side of Acid Suppression: Exploring Mood Changes in Omeprazole treated Mice

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ARTICLE INFO

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Received: *21-10-2024*
Accepted: *10-12-2024*
Published: *16-12-2024*

Keywords. *Depression, Omeprazole, Albino Mice, Immobility Time.*

ABSTRACT

Depression is considered as one of the most common major health obstacles in the communities, according to World Health Organization (WHO) about 3.8% of population are suffering from depression. The prevalence of depression in Libya is 23.68%, excluding other mental and psychiatric disorders. Few studies and experiments bay attention about the significance of pharmacological cause of depression. The researchers have turned their focus to the association between Proton pump inhibitors (PPIs) and depression and suicidal attempts, which are considered as one of the most common prescribed drugs and can be sold without prescriptions in some nations. The aim of Study is assessment omeprazole's possible depressive-like effects on experimental animals. Behavioral tests: the tail suspension test (TST), forced swim test (FST), and sucrose preference test (SPT) were used to evaluate different behavioral changes in male Swiss albino mice after they were given omeprazole (40 mg/kg) for 15 days. According to our findings, the omeprazole (40 mg/kg) had a significant effect ($p < 0.01$) on the tail suspension test and the forced swim test, and both tests had longer immobility times. An indicator of anhedonia, sucrose preference, was dramatically reduced by omeprazole (p value < 0.01). A one-way ANOVA of the body weight data showed that it was not significant ($p > 0.05$). Concerns about the long-term use of omeprazole are raised by the depressive-like effects seen in this study, especially in patients who may be taking the drug for longer periods of time. However, the supporting evidence remains limited, necessitating further research to comprehensively understand the implications of these drugs on mental health.

Cite this article. *Elbadri S, Elmasalti A, Elzulitini K. The Dark Side of Acid Suppression: Exploring Mood Changes in Omeprazole-Treated Mice. Department of Pharmacology, Faculty of Medicine, University of Benghazi, Libya. Alq J Med App Sci. 2024;7(4):1531-1539.* *https://doi.org/10.54361/ajmas.247486*

INTRODUCTION

Depression is one of the most common major health obstacles in the communities, according to World Health Organization (WHO) about 3.8% of population are suffering from depression. Approximately 700000 people each year are dying because of suicide [1]. Anew study showing the prevalence of depression in Libya is 23.68%, excluding other mental and psychiatric disorders [2]. Clinical features of depression vary among individuals from mild and temporary symptoms into severe

psychiatric illness, so depressed person feels of sadness, loss of interest, hopelessness, helplessness, also sleep disturbance, loss of appetite, feeling of guilty and suicidal thoughts]3[. The pathophysiology of this disease is covered by significant number of theories comprise: biogenic amines hypothesis, abnormality in hypothalamic pituitary adrenal axis, inflammatory mediators and immune system involvement, and genetic factors [4-7].

It has been found that acid sphingomyelinase/ceramide system and accumulation of ceramide in hippocampus plays important role in etiology of major depression [8]. However, all of these theories couldn't explore the exact molecular etiology of depression. This may explain the wide variety of anti-depressant medications are involved in treatment of depression, for example, selective serotonin reuptake inhibitors (SSRIs), Tricyclic antidepressants (TCAs), monoaminoxidase inhibitors (MAOIs), norepinephrine and dopamine reuptake inhibitor (Bupropion), and sub-anesthetic doses of ketamine has been used to treat acute cases [9-10]. All these medications unable to perform total curability from disease in many patients, and cause large number of adverse effects [11]. Economically pharmacotherapy beside psychotherapy may exhaust the budget of the citizens especially in developing countries.

The pathogenesis complexity of depression and challenges of the therapy augment the scientific research to focus on methods of prevention, and try to reduce several factors that lead to the depression such as social and psychological stress, chronic diseases, and medications [12-13]. Well-known, many medications are used for treatment of several diseases can affect mental and psychological health, and depression is an adverse effect some of these treatments [14]. Phenobarbital, barbiturate anticonvulsant, is an old example of drug inducing depressive symptoms [15]. It has been assumed that chronic use of corticosteroids was strongly related to mood disturbance [16]. Yet, few studies and experiments bay attention about the significance of pharmacological cause of depression [17].

Newly, the researchers have turned their focus to the association between Proton pump inhibitors (PPIs) and depression and suicidal attempts, which are considered as one of the most common prescribed drugs and can be sold without prescriptions in some nations [18-19]. Food and Drug Administration (FDA) has given approval for six drugs in this group which are: Omeprazole, Esomeprazole, Lansoprazole, Pantoprazole. Dexlansoprazole, and Rabeprazole [20]. They are used in treatment of gastrointestinal disease that related to acid secretion such as gastroesophageal reflex, peptic ulcer, *Helicobacter pylori* infection, and adjuvant with Nonsteroidal anti-inflammatory drugs to reduce their harmful gastric effect [21-22]. Activated forms of PPIs act by inhibiting $H^+ K^+$ ATPase, the enzyme responsible for releasing protons into the lumen of gastric gland, as a result they reduce acid secretion by 85% [23]. Common adverse effects of PPIs are nausea, constipation / diarrhea, headache, arthralgia, osteoporosis, hypergastrinemia and vitamin B12 deficiency with chronic use. Chronic kidney disease and dementia, but the two latter side effects are still under research [24].

As mentioned earlier, depression might be another adverse effect of PPIs but there are not enough studies about this effect [18]. Therefore, the study is focusing on this aspect to explore the behavioral changes, mainly depression, that might be induced by administration of omeprazole to the experimental animals. This study was conducted to evaluate the effect of proton pump inhibitors using male Swiss albino of mice as a model, and omeprazole as an example of PPIs and study their ability in inducing the depression and behavioral changes on mice.

METHODS

Animals

Male Swiss albino mice, weighing 20-40 g (8–9 weeks of age), were taken from the animal house. Mice were caged individually, five days before beginning of the actual experiment under standard temperature (27± 2 °C) with 12 h light and dark cycle for familiarization with the environment. They were free access to standard rodent diet and tap water till the end of the experiment. All behavioral activities were carried out during the light phase (10:00–14:00 h). The study was designed and conducted in accordance with the National Institute of Health (NIH) guidelines for the Care and Use of Laboratory Animals and a protocol approved by the Institutional Committee for Animal Care and Use. To avoid time and order effects all experiments were carried out in balanced design.

Drug and doses

Commercially available Omeprazole 40mg (OM) parenteral preparation, purchased locally, was used in this study. The drug was dissolved in water-for-injection (WFI) supplied along-with the parenteral preparation. It was injected intraperitoneal in

dose of 40mg/mL/kg. Control animals were injected with WFI 1 mL/kg. In the present study, OM was used in dose 40mg, this dose of OM recommended for treating gastric ulcers and reflux.

Experiment

Dose-related effects of OM on depression 20 mice were used in this experiment. The mice divided into two equal groups were assigned as; WFI treated (1 mL/kg), OM treated (40 mg/ml/kg) group. The drug or WFI were administered intraperitoneally during 10:00–10:30 h daily for 15 days. Body weights were monitored weekly. Activity in OM and control groups were monitored on day 1 and day 7; after the respective day treatment. Behavior in OM and control groups were also monitored on day 1 and day 7; after the respective day treatment.

Body weight

Change in body weight during the treatment were monitored. Percentage change in body weight was calculated as: (Body weight on day 15/starting day body weight) × 100).

Tail suspension test

Mice is suspended by its tail from a bar or beam, allowing its hind limbs to dangle freely. Immobility assessment the duration of immobility is measured over a specific time period, typically 6 minutes. Immobility is defined as the absence of any movement other than slight head or trunk movements.

The forced swim test

Water-filled container: A mouse is placed in a cylindrical container filled with water that is deep enough to prevent the animal from standing on its hind legs. The duration of immobility is measured over a specific time period, typically 6 minutes. Immobility is defined as the absence of any movement other than slight head or trunk movements.

The sucrose preference test

All animals were first trained to consume a palatable (1%) sucrose solution before the test. Then mice were deprived of water and food for 24 h. Subsequently, mice were exposed to one bottle of 1% sucrose solution and one bottle of water for 60 min, and the positions of the bottles were changed every 30 min. Before and after SPT, every bottle was weighed. The calculation formula was sucrose preference (%) = sucrose intake/ (sucrose intake + water intake) ×100%.

Statistical analysis

Results are presented as means ± SD. Statistical analysis was done by IBM SPSS Statistics version 21. One-way ANOVA was used to analyze the data on change in body weight, Independent T test was used to analyze the data on forced swimming test, tail suspension test and sucrose preference test.

RESULTS

Body weight

Figure 1 shows the effects of daily OM (40 mg/ml/kg) treatment for 15 days on body weight change. Data analyzed by One-way ANOVA revealed the drug effects were not significant for body weight $p > 0.05$.

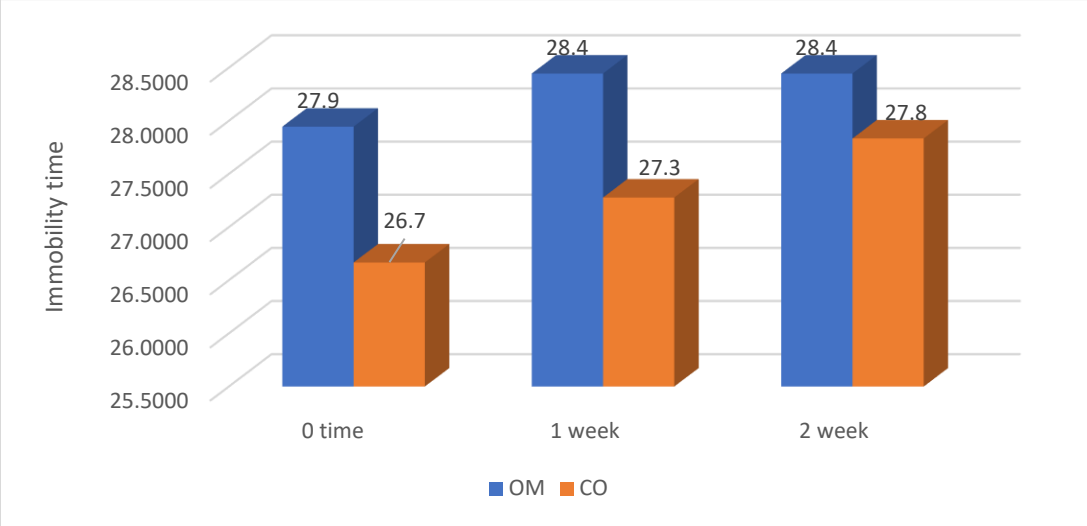

Figure 1. Weight of control group (CO) & omeprazole group (OM) during period of two weeks, which was statistically not significant.

Tail suspension test

During this test, the immobility time was more pronounced in the OM treated group rather than control group at day 7 and day 14. Data on tail suspension test was analyzed by Independent T test showed significant effect of the drug $p < 0.01$.

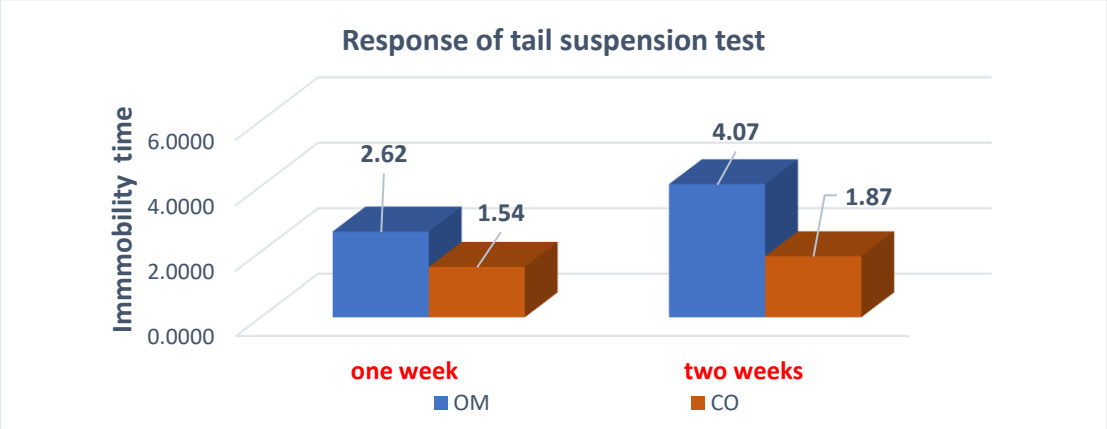

Figure 2. The immobility time of control group (CO) & omeprazole group (OM) by tail suspension test at day 7 and day 14. Which was statistically significant p value< 0.01.

Forced swim test

The results of daily OM administration 40 mg/ml/kg on immobility time by forced swim test at day 7 and day 14, appears marked difference between two groups in both days of experiment, which the immobility time increased in OM group. Data on forced swim test was analyzed by Independent T test showed significant effect of the drug $p < 0.01$ (figure3).

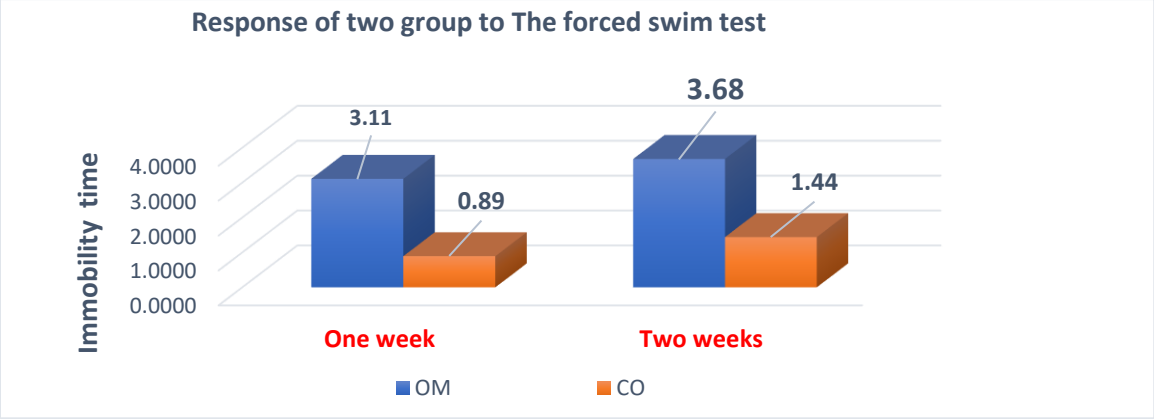

Figure 3. The immobility time of control group (CO) & omeprazole group (OM) by forced swim test at day 7 and day 14. Which was statistically significant p value < 0.01.

Sucrose preference test

The effects of 24 h of water and food deprivation on the quantity of sucrose consumed after 60 minutes, OM treated group showed less desire to consume sucrose solution than CO group. Data of the sucrose preference test was analyzed by Independent T test showed significant effect of the drug p value < 0.01 (Figure3).

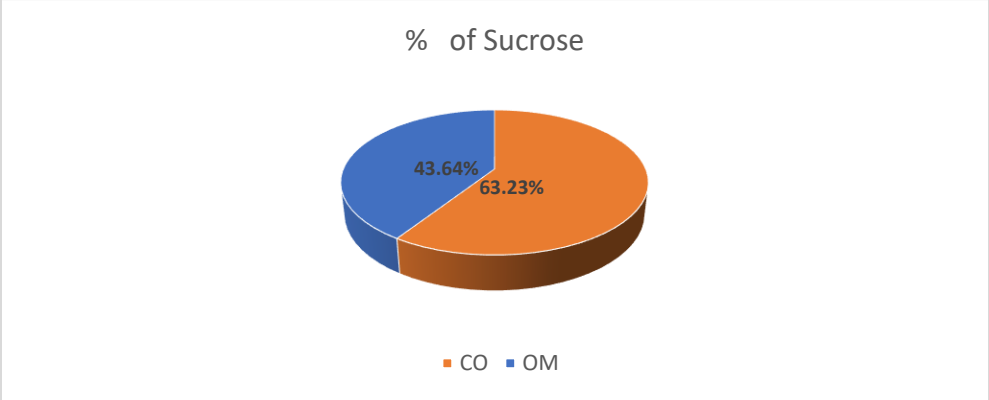

Figure (4) shows the percent of control group (CO) & omeprazole group (OM). The percent of sucrose intake of omeprazole group (OM) (43.46%) less than the percent of control group (CO) (63.23%).

DISCUSSION

The Tail Suspension Test (TST) and the Forced Swim Test (FST), two popular animal models of depressive-like behavior, were utilized in this work to investigate the effects of daily administration of omeprazole (20 mg/kg) on immobility time. The current results demonstrate that omeprazole significantly prolonged immobility time in the TST and FST on days 7 and 14, with a p-value < 0.01 for both experiments according to statistical analysis (Independent T-test). The notable rise in immobility duration seen in aforementioned behavioral tests implies that Omeprazole, at the given dosage, could trigger or intensify depressive-like behaviors in rodents. This observation is at odds with the usual outcomes of antidepressant therapies, which typically lead to a decrease in immobility duration in these models [25]. Instead, the existing findings suggest a possible depressive-like effect of omeprazole, which has not been extensively studied in earlier research.

The Tail Suspension Test (TST) and Forced Swim Test (FST) are both regarded as dependable models for assessing the behavioral impacts of antidepressants. In these tests, the amount of time spent immobile is viewed as a measure of "behavioral despair," with decreases in immobility duration usually linked to antidepressant efficacy. Conversely, an increase in immobility duration may signify a deterioration in depressive-like symptoms. these results reach agreement to previous study concluded that different omeprazole doses decrease motor activity and memory impairment in rats by using

open filed and Morris water maze tests respectively [26]. Although this previous study focused on different neurophysiological symptoms of omeprazole, it seems to be the omeprazole can produce changes in the behavior. Moreover, cross sectional study has found that the proton punmp inhibitors (PPIs) are highly associated with depression and suicidal ideation [27]. Despite, Coelho and colleagues observed the opposite results in their tail suspension experiment, and they postulated that omeprazole can improve depressive -like behavior and working memory [28]. The variances of the findings between studies provide important evidence that this group of medication has noticeable impact on central nervous system by different signals.

Additionally, the impact of 24 hours without access to food and water on sucrose intake have been assessed by the sucrose preference test during this study, which is a widely utilized method for evaluating anhedonia in rodents, and a significant indicator of depressive-like behavior by reduction in sugar intake [29]. The findings reveal that the group treated with Omeprazole (20 mg/kg) had a significant decrease in sucrose intake, consuming only 43.6% of the available sucrose, in contrast to the control group, which consumed 63.2%. An Independent T-test statistical analysis showed that the medication had a significant effect ($p < 0.01$). This raises the possibility that the medication may cause or worsen depressive-like behavior, particularly by reducing the animal's capacity to enjoy sucrose, a tasty and sweet solution.

The effect of daily treatment over a period of 15 days on body weight has been documented. The treatment with omeprazole did not lead to notable changes in body weight when compared to the control group ($p > 0.05$, analyzed using one-way ANOVA), implying that the drug's depressive-like effects seen in the tail suspension test, forced swim test, and sucrose preference test were not linked to significant variations in overall body weight.

With exception of the body weight results, all earlier observations support the idea that Omeprazole might induce a depressive-like effect, hypothetically through alterations in neurotransmitter systems or other processes within the central nervous system. As recent research elucidated that the proton pump inhibitors (PPIs), such as omeprazole, may influence the central nervous system by changing the dynamics of neurotransmitters like serotonin and dopamine which play a key role in mood regulation and emotional behavior (30). It has been detected by using the high-performance chromatography electrochemical methods, that brains of rats given OM having lower amounts of serotonin, its metabolite 5-hydroxyindoleacetic acid, and homovanillic acid a dopamine metabolite, reduced in the raphe and the hippocampal regions which can result in anxiety, depression, and cognitive decline. Besides, the expression of 5-HT-1A receptors increased in raphe and decreased in the hippocampal areas which elevates the concept of behavioral and serotonergic effects of the omeprazole [26]. Unfortunately, the molecular testing was not included during this study due to shortage of facility, and it is important to declare, there was meta-analysis included 100 studies, showed all previous experiments might not carry high rates of precision, and the objective tasks should be done to detect sensitively certain cognitive disorder [31].

The interesting hypothesis of gut brain axis (GBA) highlights how this communication can affect the physical and mental health, several studies persuasively correlate the disturbance in gut microbiota and depression incidence, by alteration in neurotransmitters levels that influence brain function through the gut-brain3 axis [32-33]. Indeed, a new approach using probiotics in treatment of major depression as adjuvant medications [34]. The prolonged exposure of rodents to omeprazole altered the levels of heathy microbiota [35]. This might explain the mechanism of depressive and behavioral consequences of omeprazole in both experimental animals and humans.

Furthermore, it has been postulated that PPIs can alter stomach acid and reduce the absorption of minerals such as magnesium, therefore long-term therapy with PPIs can cause hypomagnesemia [36]. Magnesium is an essential component in over 300 enzymatic reactions in human body, as a result, magnesium deficiency can cause neurological, cardiovascular, and musculoskeletal disorders [37]. A meta-analysis found a 1.3 times increased risk of depression in people with hypomagnesemia [38].

Although the exact way in which omeprazole induces depressive-like effects is not well understood, it is possible that its influence on neurotransmission or gut-brain communication could play a role in the behavioral changes observed [39].

CONCLUSION

Although Omeprazole is frequently prescribed for gastrointestinal issues, its potential neuropsychiatric side effects have not been thoroughly investigated. The depressive-like effects that observed in the present study raise concerns regarding the long-term use of Omeprazole, particularly in patients who may be on the medication for extended periods. However, the

supporting evidence remains limited, necessitating further research to comprehensively understand the implications of these medications on mental health.

Acknowledgments
The author would like to thank the pharmacology department in medicine faculty in university of Benghazi for providing all facilities.

Conflicts of Interest
The authors declare no conflicts of interest**.**

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https://journal.utripoli.edu.ly/index.php/Alqalam/index eISSN 2707-7179

الجانب المظلم لتثبيط الحمض: استكشاف التغيرات المزاجية في الفئران المعالجة بالأوميبرازول

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قسم علم الأدوية، كلية الطب، جامعة بنغازي، بنغازي، ليبيا

المستخلص

يُعتبر الاكتئاب أحد أكثر العقبات الصحية شيوعًا في المجتمعات، ووفقًا لمنظمة الصحة العالمية يعاني حوالي 3.8٪ من السكان من الاكتئاب. وتبلغ نسبة انتشار الاكتئاب في ليبيا 23.68٪، مع استثناء الاضطرابات العقلية والنفسية الأخرى. القليل من الدراسات والتجارب ركزت على الأهمية المحتملة للأسباب الدوائية للاكتئاب. وقد وجه الباحثون اهتمامهم نحو العلاقة بين مثبطات مضخات البروتون والاكتئاب ومحاولات الانتحار، حيث تُعتبر هذه الأدوية من بين الأكثر شيوعًا في الوصفات الطبية، كما يمكن بيعها بدون وصفة طبية في بعض البلدان. يهدف البحث إلى تقييم التأثيرات المحتملة المشابهة للاكتئاب الناتجة عن استخدام دواء الأوميبرازول على الحيوانات التجريبية. تم استخدام اختبارات سلوكية: اختبار التعليق الذيل، اختبار السباحة القسرية، واختبار تفضيل السكروز لتقييم التغيرات السلوكية المختلفة لدى ذكور الفئران السويسرية البيضاء بعد إعطائها جرعة من الأوميبرازول (40 مجم/كجم) لمدة 15 يومًا.تشير النتائج إلى أن الأوميبرازول (40 مجم/كجم) كان له تأثير ملحوظ ($p < 0.01$) على اختبار التعليق الذيل واختبار السباحة القسرية، حيث أظهرت كلا الاختبارين زيادة في أوقات الجمود. كما أن تفضيل السكروز، وهو مؤشر على فقدان الاستمتاع (أنهدونيا)، انخفض بشكل كبير بسبب تأثير الأوميبرازول ($p < 0.01$).أظهرت نتائج تحليل التباين الأحادي لبيانات وزن الجسم أنها لم تكن ذات دلالة إحصائية ($p > 0.05$). تثير هذه الدراسة القلق بشأن الاستخدام طويل الأمد للأوميبرازول، نظرًا للتأثيرات المشابهة للاكتئاب التي لوحظت، خاصة لدى المرضى الذين قد يتناولون الدواء لفترات طويلة. ومع ذلك، لا تزال الأدلة الداعمة محدودة، مما يستدعي إجراء المزيد من الأبحاث لفهم التأثيرات المحتملة لهذه الأدوية على الصحة العقلية بشكل شامل.

الكلمات المفتاحية. الاكتئاب، أوميبرازول، الفئران البيضاء، وقت عدم الحركة.