JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY 2015, 66, 5, 665-671
www.jpp.krakow.pl

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EFFECTS OF FLUOXETINE AND MELATONIN ON MOOD, SLEEP QUALITY AND BODY MASS INDEX IN POSTMENOPAUSAL WOMEN

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Frequent mood and sleep disorders and increased appetite leading to obesity are observed in postmenopausal women. Due to the limitations of hormone replacement therapy the researchers look for other treatment regimes. The aim of the study was to evaluate the efficacy of fluoxetine and melatonin in the treatment of these disorders.The study included 64 overweight postmenopausal women, aged 54 – 65 years, with increased appetite. They were randomly assigned in 2 groups. In group I (n = 30) fluoxetine (20 mg in the morning) and placebo (in the evening) were administered for 24 weeks. Group II (n = 34) received fluoxetine (20 mg in the morning) and melatonin (5 mg in the evening) in the same period of time. Hamilton anxiety rating scale (HARS), Beck depression scale (BDI), the insomnia severity index (ISI) and body mass index (BMI) were used to assess the health status and the treatment efficacy. After 24 weeks, comparable and statistically significant reduction in the level of anxiety and depression was obtained in both groups. In group I, the ISI decreased from 14.9 ± 2.5 points to 10.9 ± 1.9 points ($P < 0.05$) and in group II from 15.8 ± 2.4 points to 7.7 ± 1.5 points ($P < 0.001$). In group I no reduction in BMI was achieved whereas in group II this index decreased from 30.9 ± 3.1 to 26.3 ± 3.2 ($P < 0.05$). We conclude that combined administration of fluoxetine and melatonin was useful option to treat mood, sleep and appetite disorders in postmenopausal women.

Key words: *menopause, appetite disorders, body mass index, fluoxetine, melatonin, anxiety, depression, sleep quality*

INTRODUCTION

A variety of psychosomatic changes are observed in postmenopausal women. They include deterioration of mood, uneasiness, anxiety, sleep disorders, impaired concentration and memory (1). These changes are associated with estrogen deficiency, but other, i.e. environmental and cultural factors, are also important.

Some postmenopausal women develop depression with psychomotor retardation, decreased interest and life activity (2, 3). The picture of menopausal depression is masked by somatic symptoms, often related to the digestive system. These women experience increased appetite with nocturnal hunger and abdominal pain which leads to the development of hyperalimentation syndrome and obesity. Eating disorders are also influenced by hormones and are usually associated with the patient's mental disorders. (4). For these reasons, it is justified to use hormone replacement therapy in postmenopausal period (5). However, the use of female sex hormones has limitations due to their side effects, including as serious ones as blood clots and embolisms, heart attacks, strokes or cancer (6-10). Moreover, long-term use of estrogens and gestagens contributes to weight gain (11, 12).

Various methods are used in the treatment of obesity, including appropriately increased physical activity, psychotherapy, reducing diets and pharmacotherapy (13-17). Different dietary supplements are recommended but strong pharmaceutical agents, "hidden" from the patients, may be found in their composition. In recent years, the FDA has compiled a „blacklist" of dozens of dietary supplements that besides herbal ingredients contain drugs such as sibutramine, furosemide, bumetanide, rimonabant or phenytoin (18). These drugs used in an uncontrolled manner can cause very serious side effects. Some of them (rimonabant) are not approved for marketing in the United States and others (sibutramine) were withdrawn from the list of drugs due to the risk of serious cardiovascular events. From this list only fluoxetine - a selective secretion reuptake inhibitor has gained recognition (19, 20). It is the only drug from the SSRI which has been registered in the United States for the treatment of bulimia and metabolic syndrome (21). Fluoxetine is applied mainly in the treatment of depression, but reduction of appetite and body weight are listed among its effects. Such effects of fluoxetine may be beneficial in the case of the coexistence of obesity and depression (22).

In our previous studies conducted in postmenopausal women we did not achieve permanent anorexic effect after fluoxetine administration. The patients experienced decreased appetite in the first 2 – 3 months of the treatment but with time this effect diminished and after 6 months both the appetite and BMI increased almost to the baseline level (23). The mechanism of this 'phase' effect of fluoxetine on appetite is not clear, because the functions of the serotonergic system are complex and coupled with other neuromodulators (24, 25).

Melatonin can act synergistically with serotonin in the process of nutrition. Beneficial effects of melatonin on the

carbohydrate and lipid metabolism (26-30), as well as supression of appetite, weight loss after its suplementation were detected in animals (31-33). Clinical studies also demonstrated a correlation between low level of melatonin and obesity (34, 35) and suggested its use for therapeutic purposes (36-38). However, melatonin and its analogues exert antidepressant activity (39, 40). The reduced melatonin level could increase the risk of depresion (41) although the results of meta-analysis are not clear (40). Moreover some findings suggest the usefulness of use melatonin in combination with other antidepressants in treatment for major depressive disorder (42). The secretion of both serotonin and melatonin is suppressed in postmenopausal women which can result in emotional and eating disorders (43-46). All of the above facts point to the need of its use in the complex treatment of mood and eating disorders.

The aim of our study was to evaluate the effect of the combined administration of fluoxetine and melatonin on mood, sleep quality and body mass index in postmenopausal women.

MATERIAL AND METHODS

Patients

Sixty four women, aged 54 – 65 years (mean age 57.2 ± 4.9 years) were enrolled into the study. The patients were recruited from the Menopause Outpatient Clinic in 2007 – 2013 years. The study was conducted in Department of Clinical Nutrition and Gastroenterological Diagnostics of Medical University in Lodz (Poland) in the same time. The clinical examination included the measurement of the body height and weight used to calculate the body mass index (BMI) and psychosomatic symptoms according Greene climacteric scale.

The patients qualified for the study gave their written consent. The approval of the Bioethics Committee of the Medical University of Lodz was also obtained. The investigations were performed in accordance with the principles of the Declaration of Helsinki and according to the CONSORT guidelines for randomised trials with parallel groups.

Experimental procedures

The level of anxiety was determined using the Hamilton anxiety rating scale (HARS) and the severity of depression using the Beck depression inventory (BDI). Sleep quality was determined according to the insomnia severity index (ISI) in own modification, replacing the evaluation of the quality of life (0 – 4 scores) respectively with the 4-score assessment of the shortening of the sleeping time.

Laboratory tests comprised: blood cell count, serum levels of urea, creatinine, glucose, glycosylated hemoglobin, cholesterol, triglycerides, amylase, lipase, bilirubin, alanine and aspartate aminotransferase, thyroid stimulating hormone (TSH), 17-β-estradiol (Ortho-Clinical Diagnostics - Johnson and Johnson Co. kit) and follicle-stimulating hormone - FSH (Vitros Product antibodies).

Inclusion criteria: minimum 3 years after the menopause, increased appetite minimum 5 points in the 10-points VAS scale, overweight minimum 15% of the normal weight, low level of 17-β-estradiol and the highest level of follicle-stimulating hormone, psychological and somatic symptoms in particular anxiety, the lowest mood, insomnia, increased appetite, hunger and nocturnal epigastric pain.

Exclusion criteria: severe symptoms of anxiety (over 30 points of HARS) and depression (over 25 points of BDI scale), other mental diseases, diabetes, hypertension and other diseases requiring pharmacotherapy, the use of hormonal replacement therapy.

After the preliminary examinations the patients were randomly alloted into two groups.

Group I (n = 30) was administered for 6 months fluoxetine (1 × 20 mg in the morning) and placebo (in the evening) and group II (n = 34) fluoxetine (1 × 20 mg in the morning), and melatonin (5 mg in the evening). Packs of drugs were prepared by one of the physicians in Department of Clinical Nutrition and the blinded nurse delivered it to patients. Furthermore, a standardized diets of 1500 kcal were recommended; diets were prepared using ALIANT programme. The follow-up appointments were scheduled at week 2, 4, 8, 12, 16, 20 and 24. The extended tests were performed before and 12 and 24 weeks after the treatment and they included the assessment of the level of anxiety and depression, quality of sleep and BMI.

Statistical analysis

The statistical analysis was conducted by the Mann-Whitney test because the distribution of the most initial values of parameters in both groups were showed. ANOVA Friedman test was used to compare mean results of these groups in the time intervals. The results are presented as mean values and standard deviations. Calculations were performed with STATISTICA 9.1 software (AxAP106E735914191-F license, StatSoft Inc., Cracow, Poland).

Table 1. General characteristics and initial results of women enrolled in the study.

Feature	Group I (n = 30)	Group II (n = 34)
Age (years)	56.10 ± 5.8	57.9 ± 5.50
BMI (kg/(height in m)^2)	30.12 ± 3.51	30.92 ± 3.19
HARS (points)	23.46 ± 3.66	21.86 ± 3.24
BDI (points)	20.20 ± 2.73	19.40 ± 2.52
ISI (points)	14.93 ± 2.51	15.83 ± 2.46
17-β-estradiol (pg/ml)	16.23 ± 5.12	14.65 ± 5.45
FSH (mlU/ml)	84.60 ± 19.46	87.23 ± 18.70

Group I: patients taking fluoxetine and placebo; Group II: patients taking fluoxetine and melatonin; differences statistically insignificant.
BMI - body mass index, HARS - Hamilton anxiety scale, BDI - Beck depression inventory, ISI - insomnia severity index, FSH - follicle-stimulating hormone.

RESULTS

General characteristic of postmenopausal woman in both groups is presented in *Table 1*. Another results of laboratory tests were contained in normal limits.

Both evaluated drugs, fluoxetine and melatonin, appeared to be effective in the treatment of emotional disorders in the investigated groups of women.

Antianxiety efficacy of the applied agents was similar in both groups. In patients taking fluoxetine with placebo (group I) the level of anxiety decreased from 23.5 ± 3.6 points to 18.4 ± 3.4 points after 12 weeks ($P < 0.05$) and to 13.1 ± 3.2 points after 24 weeks ($P < 0.001$).

In patients administered fluoxetine with melatonin (group II), the level of anxiety was respectively: 21.9 ± 3.2points, 15.5 ± 2.9 ($P < 0.01$) and 12.5 ± 3.2 ($P < 0.001$); (*Fig. 1*), the differences between the groups in all time intervals were statistically insignificant.

Good effects were also obtained in the treatment of depression. In group I the level of depression decreased from 20.2 ± 2.7 points to 15.7 ± 3.5 points after 12 weeks ($P < 0.01$) and to 9.8 ± 1.8 points after 24 weeks ($P < 0.001$). In group II the level of depression was respectively: 19.4 ± 2.5 points, 15.7 ± 3.5 points ($P < 0.05$) and 9.8 ± 1.8 points ($P < 0.001$); (*Fig. 2*), the differences between the groups were statistically insignificant.

The improvement in the sleep quality was also obtained after fluoxetine. The sleep quality index decreased from 14.9 ± 2.5 points to 12.9 ± 2.6 points after 12 weeks ($P < 0.05$) and to 10.9 ± 1.9 points after 24 weeks ($P < 0.01$).

In group II taking fluoxetine combined with melatonin the improvement of the sleep quality was faster and it was respectively: 15.8 ± 2.4 points, 9.4 ± 2.0 points ($P < 0.01$) and 7.7 ± 1.5 points ($P < 0.001$); (*Fig. 3*), the differences between the groups after 12 and 24 weeks were statistically significant, values of test-z 4.613 and 3.352 ($P < 0.001$); (*Fig. 3*).

Worse results were obtained in the assessment of eating disorders. During the first 3 months the body weight tended to decrease in some patients (40.0%) taking fluoxetine and the mean BMI decreased slightly from 30.1 ± 3.5 to 28.5 ± 2.9 ($P >$

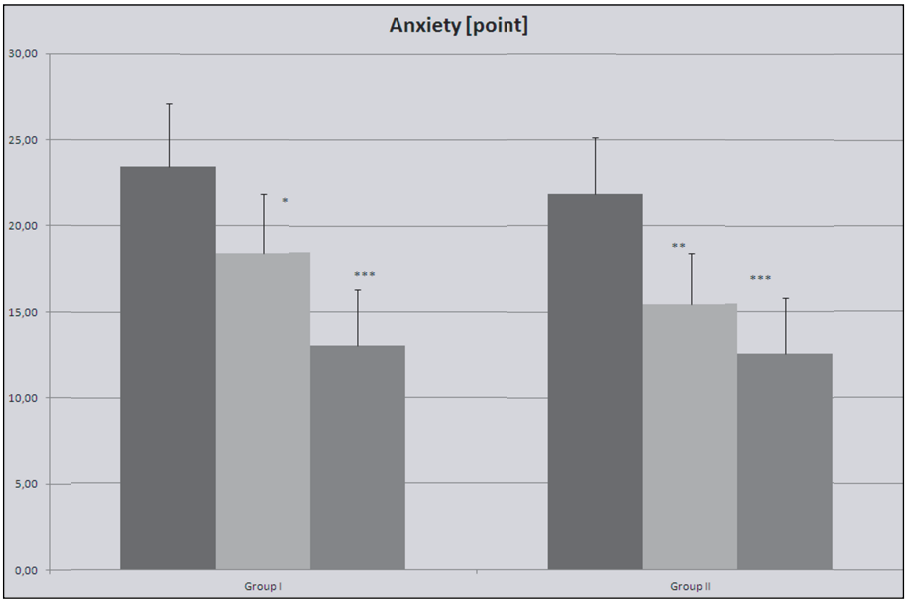

Fig. 1. The level of anxiety in group I decreased from 23.4 ± 3.6 points to 18.4 ± 4.6 points after 12 weeks (* $P < 0.05$) and to 13.1 ± 3.2 points after 24 weeks (*** $P < 0.001$). In group II anxiety decreased from 21.8 ± 3.2 points to 15.5 ± 2.9 (** $P < 0.01$) after 12 weeks and to 12.5 ± 3.2 (*** $P < 0.001$) after 24 weeks.

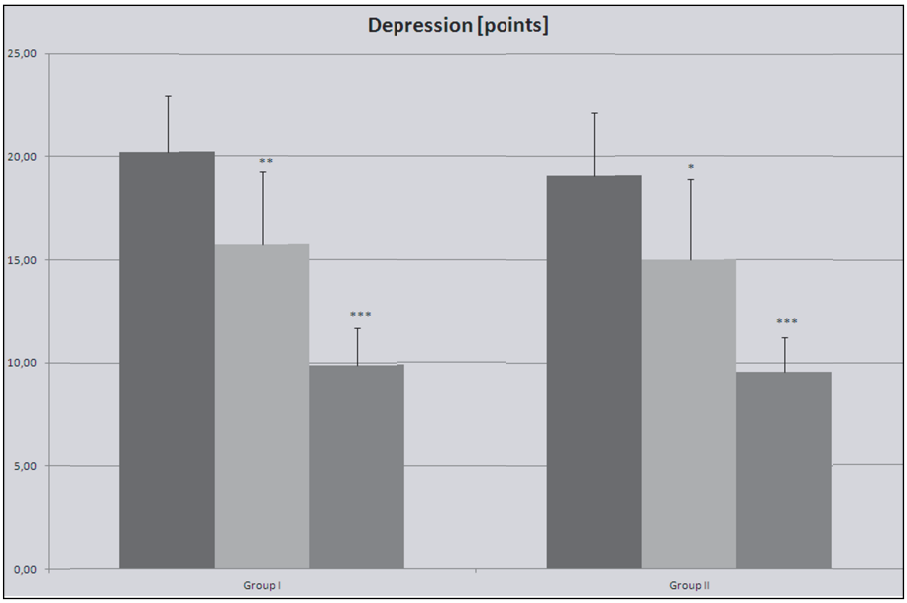

Fig. 2. The level of depression in group I decreased from 20.2 ± 2.7 points to 15.7 ± 3.5 points after 12 weeks (** $P < 0.01$) and to 9.8 ± 1.8 points after 24 weeks (*** $P < 0.001$). In group II the level of depression decreased from 19.4 ± 2.5 points to 15.0 ± 3.8 points (* $P < 0.05$) after 12 weeks and to 9.5 ± 1.6 points (*** $P < 0.001$) after 24 weeks.

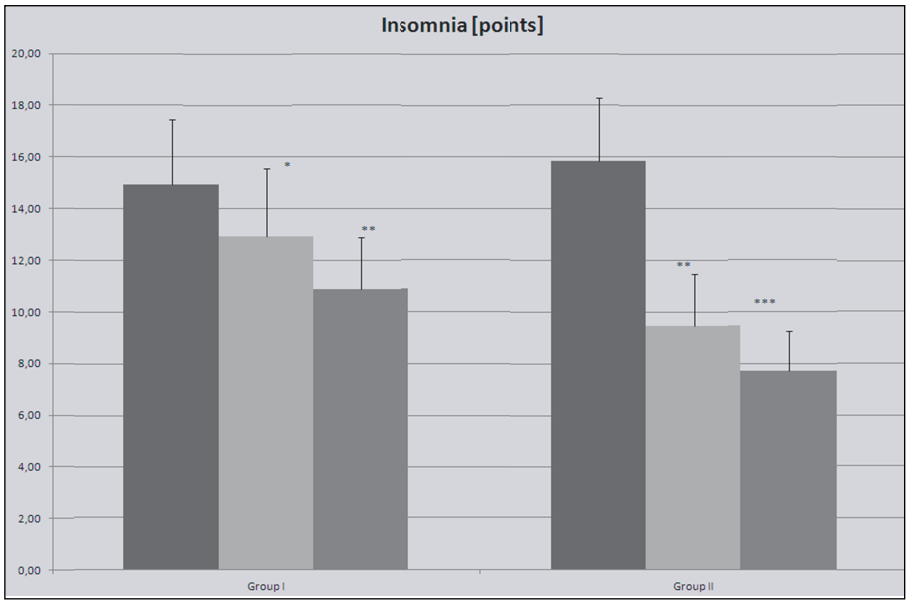

Fig. 3. The sleep quality index in group decreased from 14.9 ± 2.5 points to 12.9 ± 2.6 points after 12 weeks (* $P < 0.05$) and to 10.9 ± 1.9 points after 24 weeks (** $P < 0.01$). In group II the level of insomnia decreased from 15.8 ± 2.4 points to 9.4 ± 2.0 points ** $P < 0.01$) after 12 weeks and 7.7 ± 1.5 points (*** $P < 0.001$) after 24 weeks.

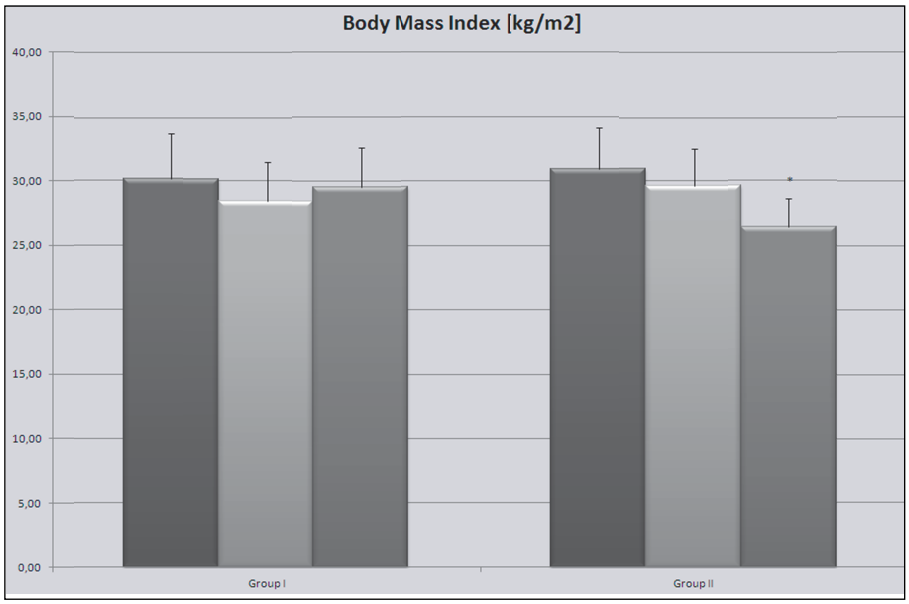

Fig. 4. The mean BMI in group decreased slightly from 30.1 to 28.5 ± 2.9 kg/(height in m)^2 ($P > 0.05$) after 12 weeks and after 24 weeks the BMI returned to the baseline value 29.5 ± 3.1 ($P > 0.05$). In group II the BMI decreased from 30.9 ± 3.1 to 29.6 ± 2.8 ($P > 0.05$) after 12 weeks and 26.3 ± 3.2 (* $P < 0.05$) after 24 weeks.

0.05), but after 24 weeks the BMI returned to the baseline value 29.5 ± 3.1 ($P > 0.05$).

Better results were observed in patients receiving fluoxetine with melatonin; in this group the BMI decreased in the same time intervals from 30.9 ± 3.1 to 29.6 ± 2.8 ($P > 0.05$) and 26.3 ± 3.2 ($P < 0.05$); (*Fig. 4*); the differences between the groups after 24 weeks were statistically significant, values of test-z 3.918 ($P < 0.001$).

Both drugs were well tolerated. In group I some of the patients reported dry mouth (36.6%) and appetite suppression (46.6%) but only during the first 8 weeks of the treatment.

Similar symptoms, i.e. dry mouth and distinct appetite suppression (47.0%) were reported by group II patients. In this group decreased appetite was maintained in varying degrees in 67.6% of the patients until the end of the therapy. Dry mouth as fluoxetine adverse events was registered in Adverse Drugs Reaction Monitoring Center.

At the same time, group II patients felt improvement of sleep quality and alleviation of somatic symptoms, particularly abdominal hunger and nocturnal pain. Compliance was very good, none drug was allowed or forbiden during the study.

DISCUSSION

The results of this study justifies the use of fluoxetine and melatonin for therapy of mood and eating in postmenopausal woman. In these cases monotherapy is recommended but the choice of suitable drugs is not always easy. In general, new generation drugs are selected, particularly serotonin reuptake inhibitors (47). It is a fairly large group of drugs that are of complex mechanism of action. Most of them are also dopamine and noradrenaline reuptake inhibitors and/or have affinity for serotonin (5-HT1A, 5-HT2), dopaminergic (D1, D2), adrenergic (α1, α2, and β), histamine, cholinergic, benzodiazepine and opioid receptors (48, 49). Fluoxetine does not manifest this multidirectional action. It only selectively inhibits serotonin reuptake in presynaptic neurons. It is effective in the treatment of anxiety-depressive disorders and also in eating disorders (50, 51). It is used, among others, in the treatment of bulimia, at a daily dose of 40 – 80 mg (52). Fluoxetine not only improves the mental state but also inhibits symptoms of bulimia nervosa. The treatment is carried out under the strict supervision of psychiatrists because in some patients fluoxetine can lead to anorexia nervosa (53, 54).

Lower doses, usually 20 mg daily, are used in the case of other emotional and metabolic disorders. Such doses, used on long-term basis also in our study, demonstrated antidepressant and anxiolytic effect. Other researchers observed suppressed appetite and weight loss after 3-month administration of fluoxetine at a daily dose of 20 mg (55). The mechanism of appetite suppression by fluoxetine is not fully recognized, but it is mainly associated with the change in the homeostasis of the serotonergic system. Fluoxetine, inhibiting the reuptake of serotonin, increases its tissue concentration and improves the neurotransmission in the CNS (56). Serotonin has a direct inhibitory effect on hunger centers in the CNS and its deficiency leads to increased appetite (50, 57, 58). That condition is present in postmenopausal women. The results of HOMDEP-MENOP Study (individualized homeopathic treatment and fluoxetine for moderate to severe depression in peri- and postmenopausal women) shown, that fluoxetine could improve depression in climacteric women. Pinto-Meza *et al*. raported that in postmenopausal woman the response for antidepressive therapy is worse (59). This may be related to the fact, that estrogens enhance serotoninergic activity. The fluoxetine is considered to be next-line option therapy if patient fails other treatment. Moreover fluoxetine is of 5-HT_{2C} receptors inhibitor, which cause among others the weight loss. (60).

Furthermore, serotonin exerts inhibitory effect on HCl secretion (61, 62) and stimulates secretion of bicarbonates in the duodenum (63, 64). Estrogens have similar activity in this regard (65, 66) and they additionally impair gastric motility (67, 68). Thus, it may be concluded that the reduced levels of estrogens and serotonin in postmenopausal women can result in increased gastric secretory and motor activity and increase the feeling of hunger as well as promote the development of hyperalimentation, which can be prevented by using fluoxetine.

Anorexic effect of fluoxetine is diminished by its long-term administration - which was observed in our research studies, but the reasons for this phenomenon are not clear. Further decrease in the level of estrogens and other hormones, including melatonin, might be one of them. Experimental studies have demonstrated that melatonin also inhibits the secretion of hydrochloric acid and pepsin (69) and stimulates the secretion of bicarbonates in the duodenum and pancreas (70). Moreover, beneficial effects of melatonin on suppression of appetite and weight loss after its supplementation were detected in animals (71, 72). Clinical studies also demonstrated a correlation between low level of melatonin and obesity with its complications and suggested its use for therapeutic purposes (73-75).

Our results confirm the positive effect of melatonin in the regulation of appetite in postmenopausal women. Particularly good results were obtained in women taking fluoxetine and melatonin, which was also reflected in the improvement of the mental status and quality of sleep. Sleep deepening and lengthening eliminated the phenomenon of ‘night snacking’, which can be an important factor in the development of obesity. Some observations indicating the stimulatory effect of fluoxetine on melatonin secretion can also explain synergistic effect of both drugs (76-78).

In conclusion, it should be stated that combined administration of fluoxetine and melatonin is an alternative option in the prevention and treatment of emotional nutritional disorders in postmenopausal women. This conclusion can be also applied to dietary treatment because melatonin is found in many food products and it can exert a beneficial effect on the regulation of metabolic processes through its antioxidant activity (73, 74, 79).

Acknowledgments: The study was supported by the grant of The Ministry of Science and Higher Education in Poland, (NN-4025437/40).

Conflict of interests: None declared.

REFERENCES

1. Freeman EW, Sammel MD, Lin H, Nelson DB. Associations of hormones and menopausal status with depressed mood in women with no history of depression. *Arch Gen Psychiatry* 2006; 63: 375-382.
2. Frey BN, Lord C, Soares CN. Depression during menopausal transition: a review of treatment strategies and pathophysiological correlates. *Menopause Int* 2008; 14: 123-128.
3. Freeman EW. Associations of depression with the transition to menopause. *Menopause* 2010; 17: 823-827.
4. Shinozaki G, Kumar Y, Rosen BH, Rundell JR, Mrazek DA, Kung S. ‘Diminished’ association between the serotonin transporter linked polymorphism (5HTTLPR) and body mass index in a large psychiatric sample. *J Affect Disord* 2013; 151: 397-400.
5. de Villiers TJ, Gass ML, Haines CJ, *et al*. Global Consensus Statement on menopausal hormone therapy. *Climacteric* 2013; 16: 203-204.
6. Rossouw JE, Prentice RL, Manson JE, *et al*. Postmenopausal hormone therapy and risk of cardiovasculardisease by age and years since menopause. *JAMA* 2007; 297: 1465-1477.
7. Archer DF, Oger E. Estrogen and progestogeneffect on venous thromboembolism in menopausal women. *Climacteric* 2012; 15: 235-240.
8. Speroff L. Transdermal hormone therapy and the risk of stroke and venous thrombosis. *Climacteric* 2010; 13: 429-432.
9. Lobo RA. Menopause and stroke and the effects of hormonal therapy. *Climacteric* 2007; 10: 27-31.
10. Antoine C, Ameye L, Paesmans M, Rozenberg S. Treatment of climacteric symptoms in breast cancer patients: a retrospectivestudy from a medication data bank. *Maturitas* 2014; 78: 2282-2232.
11. de Villiers TJ, Pines A, Panay N, *et al*. Updated 2013 International Menopause Society recommendations on menopausal hormone therapy and preventive strategies for midlife health. *Climacteric* 2013; 16: 316-337.
12. Meirelles RM. Menopause and metabolic syndrome. *Arq Bras Endocrinol Metabol* 2014; 58: 991-996.
13. Bray GA. Drug insight: appetite suppressants. *Nat Clin Pract Gastroenterol Hepatol* 2005; 2: 89-95.
14. Hainer V, Kabrnova K, Aldhoon B, Kunesova M, Wagenknecht M. Serotonin and norepinephrine reuptake inhibition and eating behavior. *Ann NY Acad Sci* 2006; 1083: 252-269.
15. Pagotto U, Vanuzzo D, Vicennati V, Pasquali R. Pharmacological therapy of obesity. *G Ital Cardiol* (*Rome*) 2008; 9: 83S-93S.
16. Bello NT, Liang NC. The use of serotonergic drugs to treat obesity - is there any hope? *Drug Des Devel Ther* 2011; 5: 95-109.
17. Resch M, Jako P, Sido Z, Haasz P. [The combined effect of psychotherapy and fluoxetine on obesity]. *Orv Hetil* 1999; 140: 2221-2225.
18. Voelker R. FDA expands warning on diet products. JAMA 2009; 301: 1646.
19. Couturier J, Lock J. A review of medication use for children and adolescents with eating disorders. *J Can Acad Child Adolesc Psychiatry* 2007; 16: 173-176.
20. Leombruni P, Piero A, Lavagnino L, Brustolin A, Campisi S, Fassino S. A randomized, double-blind trial comparing sertraline and fluoxetine 6-month treatment in obese patients with Binge Eating Disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 2008; 32: 1599-1605.
21. Jackson CW, Cates M, Lorenz R. Pharmacotherapy of eating disorders. *Nutr Clin Pract* 2010; 25: 143-159.

22. Greeno CG, Wing RR. A double-blind, placebo-controlled trial of the effect of fluoxetine on dietary intake in overweight women with and without binge-eating disorder. *Am J Clin Nutr* 1996; 64: 267-273.
23. Jalocha W, Walecka-Kapica E, Tomaszewska-Warda K, Chojnacki J, Klupinska G. The effect of fluoxetine and tianeptine on emotional and obesity disorders in postmenopausal woman. *Pol Merk Lek* 2014; 37: 35-38.
24. Leibowitz SF. The role of serotonin in eating disorders. *Drugs* 1990; 39: 33-48.
25. Owens MJ, Nemeroff CB. Role of serotonin in the pathophysiology of depression: focus on the serotonin transporter. *Clin Chem* 1994; 40: 288-295.
26. Sanchez-Mateos S, Alonso-Gonzalez C, Gonzalez A, *et al*. Melatonin and estradiol effects on food intake, body weight, and leptin in ovariectomized rats. *Maturitas* 2007; 58: 91-101.
27. Sartori C, Dessen P, Mathieu C, *et al*. Melatonin improves glucose homeostasis and endothelial vascular function in high-fat diet-fed insulin-resistant mice. *Endocrinology* 2009; 150: 5311-5317.
28. Nduhirabandi F, Du Toit EF, Blackhurst D, Marais D, Lochner A. Chronic melatonin consumption prevents obesity-related metabolic abnormalities and protects the heart against myocardial ischemia and reperfusion injury in a prediabetic model of diet-induced obesity. *J Pineal Res* 2011; 50: 171-182.
29. Srinivasan V, Ohta Y, Espino J, *et al*. Metabolic syndrome, its pathophysiology and the role of melatonin. *Recent Pat Endocr Metab Immune Drug Discov* 2013; 7: 11-25.
30. Zanuto R, Siqueira-Filho MA, Caperuto LC, *et al*. Melatonin improves insulin sensitivity independently of weight loss in old obese rats. *J Pineal Res* 2013; 55: 156-165.
31. Wolden-Hanson T, Mitton DR, McCants RL *et al*. Daily melatonin administration to middle-aged male rats suppresses body weight, intraabdominal adiposity, and plasma leptin and insulin independent of food intake and total body fat. *Endocrinology* 2000; 141: 487-497.
32. Puchalski SS, Green JN, Rasmussen DD. Melatonin effects on metabolism independent of gonad function. *Endocrinology* 2000; 141: 487-497.
33. Rasmussen DD, Boldt BM, Wilkinson CW, *et al*. Daily melatonin administration at middle age suppresses male rat visceral fat, plasma leptin, and plasma insulin to youthful levels. *Endocrinology* 1999; 140: 1009-1012.
34. Blaicher W, Speck E, Imhof MH, *et al*. Melatonin in postmenopausal females. *Arch Gynecol Obstet* 2000; 263: 116-118.
35. Sato M, Kanikowska D, Iwase S, *et al*. Seasonal differences in melatonin concentrations and heart rates during sleep in obese subjects in Japan. *Int J Biometeorol* 2013; 57: 743-748.
36. Rastmanesh R, de Bruin PF. Potential of melatonin for the treatment or prevention of obesity: an urgent need to include weight reduction as a secondary outcome in clinical trials of melatonin in obese patients with sleep disorders. *Contemp Clin Trials* 2012; 33: 574-575.
37. Nduhirabandi F, du Toit EF, Lochner A. Melatonin and the metabolic syndrome: a tool for effective therapy in obesity-associated abnormalities? *Acta Physiol* (*Oxf*) 2012; 205: 209-223.
38. Dzherieva IS, Volkova NI, Rapoport SI. Association between depression and metabolic syndrome-a two-way street. *Klin Med* (*Mosk*) 2015; 93: 62-65.
39. Laudon M, Frydman-Marom A. Therapeutic effects of melatonin receptor agonists on sleep and comorbid disorders. *Int J Mol Sci* 2014; 15: 15924-15950.
40. Hansen MV, Danielsen AK, Hageman I, Rosenberg J, Gogenur I. The therapeutic or prophylactic effect of exogenous melatonin against depression and depressive symptoms: a systematic review and meta-analysis. *Eur Neuropsychopharmacol* 2014; 24: 1719-1728.
41. Szewczyk-Golec K, Wozniak A, Reiter RJ. Interrelationships of the chronobiotic, melatonin, with leptin and adiponectin: implications for obesity. *J Pineal Res* 2015; Jun 23. doi: 10.1111/jpi.12257.
42. Targum SD, Wedel PC, Fava M. Changes in cognitive symptoms after a buspirone-melatonin combination treatment for major depressive disorder. *J Psychiatr Res* 2015; 68: 392-396.
43. Blum I, Vered Y, Lifshitz A, *et al*. The effect of estrogen replacement therapy on plasma serotonin and catecholamines of postmenopausal women. *Isr J Med Sci* 1996; 32: 1158-1162.
44. Hall E, Steiner M. Serotonin and female psychopathology. *Womens Health* (*Lond Engl*) 2013; 9: 85-97.
45. Vakkuri O, Kivela A, Leppaluoto J, Valtonen M, Kauppila A. Decrease in melatonin precedes follicle-stimulating hormone increase during perimenopause. *Eur J Endocrinol* 1996; 135: 188-192.
46. Toffol E, Kalleinen N, Haukka J, Vakkuri O, Partonen T, Polo-Kantola P. Melatonin in perimenopausal and postmenopausal women: associations with mood, sleep, climacteric symptoms, and quality of life. *Menopause* 2014; 21: 493-500.
47. Appolinario JC, McElroy SL. Pharmacological approaches in the treatment of binge eating disorder. *Curr Drug Targets* 2004; 5: 301-307.
48. Halford JC, Harrold JA, Lawton CL, Blundell JE. Serotonin (5-HT) drugs: effects on appetite expression and use for the treatment of obesity. *Curr Drug Targets* 2005; 6: 201-213.
49. Garfield AS, Heisler LK. Pharmacological targeting of the serotonergic system for the treatment of obesity. *J Physiol* 2009; 587: 49-60.
50. Molinari E, Baruffi M, Croci M, Marchi S, Petroni ML. Binge eating disorder in obesity: comparison of different therapeutic strategies. *Eat Weight Disord* 2005; 10: 154-161.
51. Baretic M. Targets for medical therapy in obesity. *Dig Dis* 2012; 30: 168-172.
52. Milano W, De Rosa M, Milano L, Riccio A, Sanseverino B, Capasso A. The pharmacological options in the treatment of eating disorders. *ISRN Pharmacol* 2013; 2013: 352865.
53. Oliveros SC, Iruela LM, Caballero L, Baca E. Fluoxetine-induced anorexia in a bulimic patient. *Am J Psychiatry* 1992; 149: 1113-1114.
54. Vaz FJ, Salcedo MS. Fluoxetine-induced anorexia in a bulimic patient with antecedents of anorexia nervosa. *J Clin Psychiatry* 1994; 55: 118-119.
55. Voznesenskaia TG, Safonova VA, Platonova NM. Disorder of eating behavior and comorbid syndromes in obesity and methods of their correction. *Zh Nevrol Psikhiatr im S.S. Korsakova* 2000; 100: 49-52.
56. Dunlop SP, Coleman NS, Blackshaw E, *et al*. Abnormalities of 5-hydroxytryptamine metabolism in irritable bowel syndrome. *Clin Gastroenterol Hepatol* 2005; 3: 349-357.
57. Halford JC, Harrold JA. 5-HT(2C) receptor agonists and the control of appetite. *Handb Exp Pharmacol* 2012; 209: 349-356.
58. Brewerton TD. Toward a unified theory of serotonin dysregulation in eating and related disorders. *Psychoneuroendocrinology* 1995; 20: 561-590.
59. Pinto-Meza A, Usall J, Serrano-Blanco A, Suarez D, Haro JM. Gender differences in response to antidepressant treatment prescribed in primary care. Does menopause make a difference? *J Affect Disord* 2006; 93: 53-60.
60. Macias-Cortes Edel C, Llanes-Gonzalez L, Aguilar-Faisal L, Asbun-Bojalil J. Individualized homeopathic treatment and

fluoxetine for moderate to severe depression in peri- and postmenopausal women (HOMDEP-MENOP study): a randomized, double-dummy, double-blind, placebo-controlled trial. *PLoS One* 2015; 10: e0118440.
61. Johansen B, Bech K. BRL 24924, a 5-hydroxytryptamine type 3 antagonist, and gastric secretion of acid and pepsin in vivo. *Digestion* 1991; 48: 121-127.
62. Lepard KJ, Chi J, Mohammed JR, Gidener S, Stephens RL. Gastric antisecretory effect of serotonin: quantitation of release and site of action. *Am J Physiol* 1996; 271: E669-E677.
63. Safsten B, Sjoblom M, Flemstrom G. Serotonin increases protective duodenal bicarbonate secretion via enteric ganglia and a 5-HT4-dependent pathway. *Scand J Gastroenterol* 2006; 41: 1279-1289.
64. Tuo B, Wen G, Wei J, *et al*. Estrogen regulation of duodenal bicarbonate secretion and sex-specific protection of human duodenum. *Gastroenterology* 2011; 141: 854-863.
65. Amure BO, Omole AA. Sex hormones, and acid gastric secretion induced with carbachol, histamine, and gastrin. *Gut* 1970; 11: 641-645.
66. Tuo BG, Sellers Z, Paulus P, Barrett KE, Isenberg JI. 5-HT induces duodenal mucosal bicarbonate secretion via cAMP- and Ca^{2+}-dependent signaling pathways and 5-HT4 receptors in mice. *Am J Physiol Gastrointest Liver Physiol* 2004; 286: 444-451.
67. Hutson WR, Roehrkasse RL, Wald A. Influence of gender and menopause on gastric emptying and motility. *Gastroenterology* 1989; 96: 11-17.
68. Bond EF, Heitkemper MM, Bailey SL. Estrogen suppresses gastric motility response to thyrotropin-releasing hormone and stress in awake rats. *Res Nurs Health* 1998; 21: 221-228.
69. Kato K, Murai I, Asai S, *et al*. Central nervous system action of melatonin on gastric acid and pepsin secretion in pylorus-ligated rats. *Neuroreport* 1998; 9: 2447-2450.
70. Sjoblom M, Flemstrom G. Melatonin in the duodenal lumen is a potent stimulant of mucosal bicarbonate secretion. *J Pineal Res* 2003; 34: 288-293.
71. Prunet-Marcassus B, Desbazeille M, Bros A, *et al*. Melatonin reduces body weight gain in Sprague Dawley rats with diet-induced obesity. *Endocrinology* 2003; 144: 5347-5352.
72. Hussein MR, Ahmed OG, Hassan AF, Ahmed MA. Intake of melatonin is associated with amelioration of physiological changes, both metabolic and morphological pathologies associated with obesity: an animal model. *Int J Exp Pathol* 2007; 88: 19-29.
73. Pierpaoli W, Regelson W. The Metabolism Miracle. New York, Simen and Schuster, 1996.
74. Kirecci SL, Simsek A, Gurbuz ZG, *et al*. Relationship between plasma melatonin levels and the efficacy of selective serotonin reuptake inhibitors treatment on premature ejaculation. *Int J Urol* 2014; 21: 917-920.
75. Chojnacki C, Walecka-Kapica E, Mokwinska M, *et al*. Influence of tianeptine on melatonin homeostasis and psychosomatic symptoms in patients with irritable bowel syndrome. *J Physiol Pharmacol* 2013; 64: 177-183.
76. Tan DX, Zanghi BM, Manchester LC, Reiter RJ. Melatonin identified in meats and other food stuffs: potentially nutritional impact. *J Pineal Res* 2014; 57: 213-218.
77. Bonnefont-Rousselot D. Obesity and oxidative stress: potential roles of melatonin as antioxidant and metabolic regulator. *Endocr Metab Immune Disord Drug Targets* 2014; 14: 159-168.
78. Zirlik S, Hildner KM, Targosz A, *et al*. Melatonin and omentin: influence factors in the obstructive sleep apnoea syndrome? *J Physiol Pharmacol* 2013; 64: 353-360.
79. Adamczyk-Sowa M, Pierzchala K, Sowa P, Polaniak R, Kukla M, Hartel M. Influence of melatonin supplementation on serum antioxidative properties and impact of the quality of life in multiple sclerosis. *J Physiol Pharmacol* 2014; 65: 543-550.

Received: December 15, 2014
Accepted: July 17, 2015

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