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, their side effects, including as serious ones as blood clots and embolisms, heart attacks, strokes or cancer (6-10). Moreover, their side effects, including as serious ones as blood clots and embolisms, heart attacks, strokes or cancer (6-10).

Patients with depression including appetite disorders were treated with fluoxetine and melatonin 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

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.

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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 phentoin (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
Experimental procedures

Groups.

The CONSORT guidelines for randomised trials with parallel groups were followed. The Declaration of Helsinki and according to the Greene climacteric scale. Body mass index (BMI) and psychosomatic symptoms according 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 (Vitro 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 allotted 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.

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

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 ± 3.2 points, 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 >
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 forbidden 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).

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).

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).

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