

PHARMACOLOGY

EFFECTS OF ANTIDEPRESSANTS AND SOYBEAN ASSOCIATION IN DEPRESSIVE MENOPAUSAL WOMEN

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Abstract: Depression in menopausal women has been widely described for many years ago, and is related to hormonal decrease, mainly estrogens. The use of soy has been proposed as a possible coadjutant alternative to treat menopausal depressive disorder. In the present pilot clinical trial the effect of soybean, antidepressants and the association of soybean with antidepressants was studied in 40 depressive menopausal women for three months. Patients were divided in four groups of 10 women: fluoxetine (10 mg), soybean (100 mg), sertraline (50 mg), and sertraline (50 mg) plus soybean (100 mg). The Hamilton and Zung Depression Scales were used to measure the treatment effects. Values at the beginning and at the end of the study were compared. In all cases a significant difference was observed when the treated groups were compared *vs.* their untreated situation in both scales ($p < 0.001$). When a comparison between pre- minus post-treatment Zung scale scores was done, the effect induced by the association of sertraline and soybean was significantly higher than the other groups ($p < 0.05$). These effects were also seen using the Hamilton scale scores, showing significant differences between the association *vs.* soybean ($p < 0.05$) and sertraline ($p < 0.05$) groups, but not *vs.* fluoxetine group. We conclude that soybean has an antidepressant effect *per se*, and the association of soybean and antidepressants increases their effects.

Keywords: menopause, depressive disorder, soybean, antidepressant, serotonin receptor inhibitor antidepressants

Menopause is a word developed from Greek roots, meaning cessation (pauses) and month (men), designing the interruption of the cyclic monthly blood flow named menstruation, corresponding to the end of fertility. This state is retrospectively fixed, after the absence of menstruation for 12 consecutive months. Technically, it is due to the loss of ovulation, and is linked to structural and functional modifications in the reproductive axis (1).

In menopause, several features valued by society, such as youth and the ability to procreate, disappear. The loss of these features can be considered psychological factors, which may predispose a woman to a depressive disorder, and the hormonal changes may contribute to these disorders, suggesting a multifactorial etiology (2). Menopausal

women are at an increased risk of developing osteoporosis (3), cardiovascular disease (4) and depressive disorders (5, 6). Actually, depressive disorders and menopause are closely related (2). Due to the fact that these modifications in hormonal levels are conditioning the psychological symptoms, it could be considered that present symptoms could be included in psychotical group in the schneiderian criteria (7). The ethiological treatment could be the hormone replaces treatment (8), but the risk of breast and endometrium cancer related to hormone replace treatment has been reported, and natural products have been suggested as a potential alternative (9).

In previous reports, the effects of treating menopause with soybean have been a matter of dis-

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discussion (9). The purpose of this study is to compare the effect of selective serotonin receptor inhibitor antidepressants (SSRI) alone, soybean alone and combination of SSRI antidepressants with soybean.

SUBJECTS AND METHODS

The sample selection was carried out with the informed consent and commitment of psychiatric patients who have been diagnosed with depression, at ages of 45 to 55, in menopause state, willing to participate in the study. Patients were referred to the psychiatric consultation from other medical specialties consultations including endocrinology, gynecology and cardiology in which depression was observed. Forty patients were chosen and were randomly divided into four groups; each group consisted of 10 patients. Because of the ethical requirements, they were informed about the experimental conditions, but not any detail was administered about medication, blinding to them the probe.

Two depression scales were used: the Zung Self-Rating Scale (10) and the Hamilton Rating Scale for Depression (HAM-D) (11). Data are referred in comparison to their corresponding percentualized baselines (means considered as 100%). This 100% corresponded to a mean of baselines of 62.50 points for the Zung scale and 19.70 for the Hamilton scale.

A pilot prospective longitudinal clinical study was performed, in which 40 menopausal depressive women between 45 to 55 years old, treated in private psychiatry practice in Santo Domingo, Dominican Republic, were included. The study was conducted during three months. Psychological tests were administered at the beginning and at the end of the three months period, for all 40 women throughout the year, which aimed to compare the scores and evaluate the results. Women were randomly assigned to 4 groups of 10 patients each. The first group received fluoxetine (10 mg). The second group received soy (100 mg daily, soy isoflavones concentrate, 50 mg, GNC Laboratories, USA). The third group received sertraline (50 mg daily). The fourth group received soy (100 mg) and sertraline (50 mg). No differences were observed between groups in age, body weight or estrogen levels. In a few cases, a low dose of hypnotics was occasionally used (alprazolam, 0.5 mg or mesazolam, 1 mg). During the three months period, patients were observed every 21 days, evaluating their treatment courses. At the end of the study, the same scales were repeated.

RESULTS

A statistical difference was observed in the treatment effects of fluoxetine (10 mg), soybean, sertraline (50 mg), and sertraline (50 mg) plus soybean on Zung (top) and Hamilton (bottom) scales evaluating pre-treatment and post-treatment scores. The four groups were compared vs. their previous pre-treatment scores. In the case of the Zung depression scale, ANOVA 1 showed significant intergroup differences ($F_{7,79} = 24.06$, $p < 0.0001$), and Newman-Keuls test revealed significant differences between pre- and post-treatment in all groups ($p < 0.001$). The Hamilton Depression Scale also showed statistical differences between groups (ANOVA 1, $F_{7,79} = 31.73$, $p < 0.0001$), and statistically significant differences were observed between pre- and post-treatment conditions in all groups (Newman-Keuls, $p < 0.001$).

The difference levels comparison (pre- versus post-treatment scores) induced by fluoxetine (10 mg), soybean, sertraline (50 mg), and sertraline (50 mg) plus soybean on Zung (top) and Hamilton (bottom) scales showed statistical differences. The differences in the scores of the four groups of ten patients each were compared. In the case of Zung depression scale, ANOVA 1 showed significant intergroup differences ($F_{3,39} = 3.911$, $p < 0.005$), and Newman-Keuls revealed significant differences between sertraline (50 mg) plus soybean and the other groups (Newman-Keuls, $p < 0.05$). The Hamilton Depression Scale also showed statistical differences between groups (ANOVA 1, $F_{3,39} = 3.716$, $p < 0.005$), and statistically significant differences were observed between sertraline (50 mg) plus soybean and soybean and sertraline (50 mg) groups (Newman-Keuls, $p < 0.05$).

DISCUSSION

Present findings show an important treatment effect in all groups. Significant difference between pre-treatment and post-treatment scores were observed in all groups post using both scales (Fig. 1). The fact that low doses had a very significant effect suggests a very sensitive population in these conditions. It must be noted that one scale was evaluated by the professional and the other by the patients. Responses coincided and were statistically significant ($p < 0.001$). It is a strong argument about the reliability of present conditions. In all cases a clear effect was observed after treatment.

When different levels (pre- minus post-treatment scores) were compared, the association of ser-

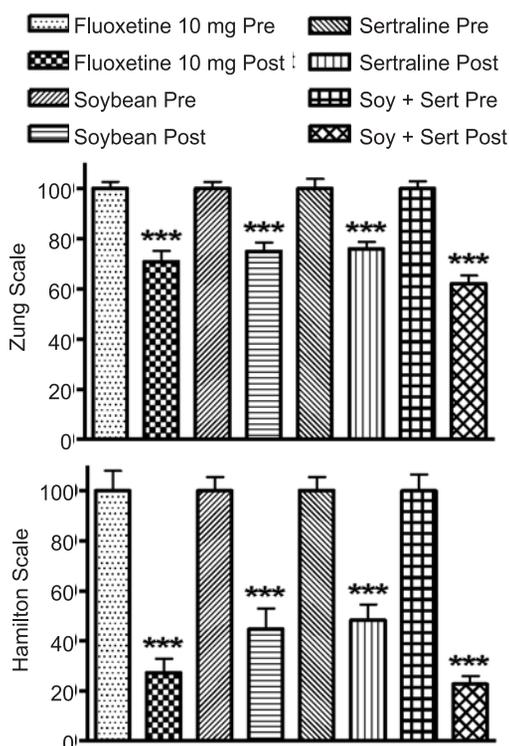


Figure 1. Comparison of treatment effects of fluoxetine (10 mg), soybean, sertraline (50 mg), and sertraline (50 mg) plus soybean on Zung (top) and Hamilton (bottom) scales evaluating pre-treatment and post-treatment scores. Four groups of 10 patients compared each one were compared vs. their previous pre-treatment scores. In the case of Zung depression scale, ANOVA 1 showed significant intergroup differences ($F_{7,79} = 24.06, p < 0.0001$), and Newman-Keuls revealed significant differences between pre- and post-treatment in all cases ($p < 0.001$). The Hamilton Depression Scale showed also statistical differences between groups (ANOVA 1, $F_{7,79} = 31.73, p < 0.0001$), and statistically significant differences were observed between pre- and post- treatment conditions in all cases (Newman-Keuls, $p < 0.001$). Data are presented as the mean \pm standard error of the mean (SEM). *** = $p < 0.001$

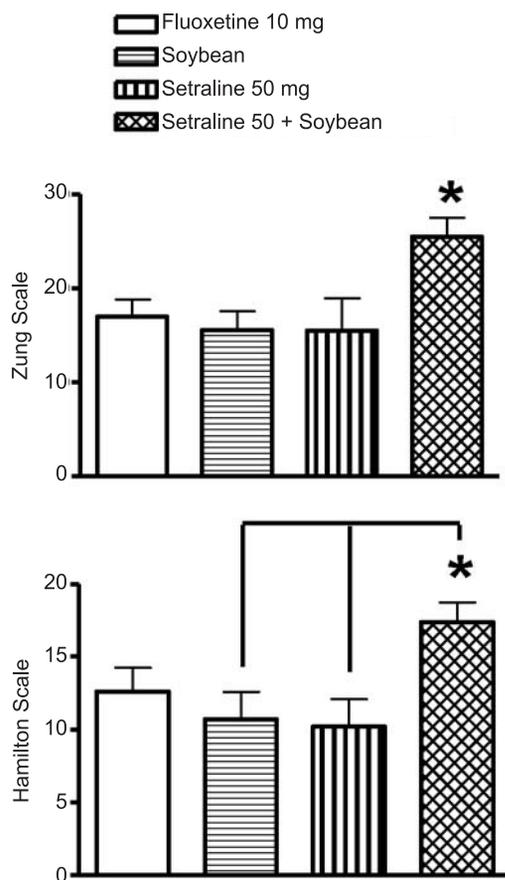


Figure 2. Comparison of the difference levels (pre- minus post-treatment scores) induced by fluoxetine (10 mg), soybean, sertraline (50 mg), and sertraline (50 mg) plus soybean on Zung (top) and Hamilton (bottom) scales. The score differences of the four groups of 10 patients each one were compared. In the case of Zung depression scale, ANOVA 1 showed significant intergroup differences ($F_{3,39} = 3.911, p < 0.005$), and Newman-Keuls revealed significant differences between sertraline (50 mg) plus soybean and the other groups (Newman-Keuls, $p < 0.05$). The Hamilton Depression Scale showed also statistical differences between groups (ANOVA 1, $F_{3,39} = 3.716, p < 0.005$), and statistically significant differences were observed between sertraline (50 mg) plus soybean and soybean and sertraline (50 mg) groups (Newman-Keuls, $p < 0.05$). Data are presented as the mean \pm standard error of the mean (SEM). * = $p < 0.05$

traline and soybean showed a significant difference with the other groups in the Zung scale (Fig. 2, top), which is auto administered. This fact provides an idea that the subjective perception of improvement was very clear, showing a very positive treatment effect impression with the association of soybean and sertraline. It could be considered as a potentiation phenomenon.

The scores observed in the Hamilton scale (Fig. 2, bottom) showed a clear difference between soybean alone and sertraline alone vs. their coadministration. It also strongly suggests a potentiation phenomenon. The fact that the difference with fluoxetine group did not reach significance could be suggesting a lower potency difference with sertraline in this group of patients. However, patients'

perception (Zung scale) maintains the idea that a significant difference actually exists.

The action of antidepressant drugs is not immediate, and a latency period is necessary to induce changes that involve integrated mechanisms, including noradrenergic and serotonergic transmission (12–14). The final effect appears to be mediated by a decrease in the number of β -adrenergic receptors and activity, measured by norepinephrine (NE) mediated stimulation of adenylate cyclase

(15). This effect appears to be induced by an increase in the synaptic concentration of NE due to a decrease of $\alpha 2$ -receptor sensitivity. It has been postulated that this decremental sensitivity modification of $\alpha 2$ adrenergic autoreceptors is the first change induced by antidepressant action (14, 16). The simultaneous administration of antidepressants and $\alpha 2$ antagonists decrease the treatment latency in experimental approaches (14).

The role of serotonergic neurons appears to be related to a tonic inhibition exerted on noradrenergic neurons (13). Imipramine has recognition sites on serotonergic neurons, and desipramine in noradrenergic sites (13). However, desipramine is a metabolite of imipramine (17). The antidepressant drugs here used are all SSRIs, acting all through serotonin neurons, and a combination of antidepressants appears to be more effective than the separate exclusive use of them (18).

The temporal sequence of changes strongly suggests the involvement of integrated mechanisms, mainly noradrenergic and serotonergic (13). The antidepressant drugs here used in the study are all SSRIs, acting all through serotonin neurons, and a combination of antidepressants appears to be more effective than the separate exclusive use of them (19). Soybean extract appears to be potentiating the effect of antidepressants here used.

As previously stated, depressive disorders in menopause have been largely clinically observed (2), and hormones decrease induces important symptoms (20). Menopausal symptoms improve after hormone replacement, with the risk of relapse after cessation of hormone replacement therapy (21, 22). Clinically, it has been reported that antidepressants alone do not ensure success in treatment of depressive disorders in menopausal women (2). Estradiol alone (transdermal estradiol replacement) has a significant antidepressive effect in perimenopausal depression (23). Recently, the effect of addition of raloxifene, a selective estrogen receptor modulator (SERM) to SSRI gave satisfactory effects inducing complete remission in a postmenopausal depressive disorder (24).

The use of some treatment alternatives to hormone replacement therapy for hot flashes in breast cancer survivors has been proposed (25, 26), including soy phytoestrogens (20, 27). Soy and social stress affect serotonin neurotransmission in primates (19). The use of soy-derived isoflavones has been proposed as a protective factor against depression starting from basic translational approaches (28). A relevant stimulatory effect of phytoestrogens on noradrenaline and serotonin transporters activity has

been reported (29). The effect of glutamatergic stimulation on sexual behaviors in rats appears to be driven by an induction of central adrenergic receptor prevalence modifications exerted by sexual hormones (30–35), similar to those induced by antidepressants. In fact, it has been reported that ovarian steroids induce modifications in noradrenergic and serotonergic receptors in the rat brain (36, 37). Furthermore, estradiol has shown a synergistic antidepressant effect with fluoxetine in animal studies of experimental depression (38).

Some side effects have been reported related to soy administration, mainly thyroid dysfunctions like goiter in infants (39). However, in adult menopausal women the soybean administration seems not to affect thyroid function (39). In adults, the most relevant problem is soy allergy (40), but benefits for treating menopausal depression, as it has been shown here, outweighs side effects of soybean administration.

In the present clinical schedule, SSRI antidepressants are acting on serotonergic transmission. The action of soybean, as homologous equivalent of hormonal replacement, could be influencing noradrenergic transmission, the final pathway. Since SSRI antidepressants are acting on serotonergic system and the soybean active principles could be acting in noradrenergic system, the potentiation here observed could be explained by a synergistic action of both treatments. Present results give more evidences regarding the action of hormones and menopausal depressive disorders.

We conclude that the administration of soybean could enhance the response to SSRI antidepressants in menopausal women, and that soybean could act as an interesting alternative to estrogens in the treatment of mood disorders during menopause.

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