

Psychological assessment of the effects of treatment with phytoestrogens on postmenopausal women: a randomized, double-blind, crossover, placebo-controlled study

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Objective: To investigate the effects of soy isoflavones on mood and cognitive function in postmenopausal women.

Design: Randomized, double-blind, cross-over, placebo-controlled trial.

Setting: University Hospital, Milan, Italy; A.G.UN.CO. Obstetrics and Gynaecology Centre, Rome, Italy.

Patient(s): Seventy-eight postmenopausal women.

Intervention(s): We administered 60 mg/day isoflavones or placebo for 6 months. After a washout period of 1 month, the patients who had been treated with phytoestrogens received placebo, and those who previously received placebo were administered phytoestrogens (for 6 months).

Main Outcome Measure(s): Cognitive performance and mood were assessed by a battery of tests at the end of each treatment period. At the end of the study, the patients were also asked whether they preferred the first or second treatment.

Result(s): The 17 scores on cognitive performance test and the 6 for mood assessments 6 showed an advantage for the treatment with phytoestrogens. Similarly, of the 8 visual analogue scales used to indicate mood, 7 improved significantly after the treatment with phytoestrogens. Moreover, 49 patients preferred phytoestrogens, 9 placebo, and 18 had no preference. The preference was not related to the order of treatment.

Conclusion(s): These results suggest that isoflavones may have positive effects on postmenopausal women improving cognitive performance and mood. (Fertil Steril® 2006;85:972–8. ©2006 by American Society for Reproductive Medicine.)

Key Words: Phytoestrogens, estrogens, mood, cognitive performance, postmenopause

The influences of estrogens (E) on the central nervous system (CNS) have been widely investigated. They exert numerous and complex interactions outside the reproductive function, including actions on brain areas that are important for learning, memory, emotions, affective state, and also motor coordination and pain sensitivity (1–3). Many studies reported the positive effects of the administration of estrogens, either alone or in combination with progestins, in significantly lowering the incidence of depressive mood and improving cognitive performance in postmenopause (4–9), although not all investigators have confirmed these findings.

Hormone therapy (HR) has been extensively used because of its beneficial effects on the aging processes in perimenopausal women, although its use has been recently questioned due to the growing concern on the occurrence of side effects (10, 11). Some alternative therapies have been proposed (e.g., the use of isoflavones, compounds naturally occurring in plant foods) that seem to confer positive effects with fewer associated adverse events than synthetic hormones (12). Isoflavones are nonsteroidal E-like substances, with a biochemical activity similar to that of E, which bind E receptors (ERs). This is the reason why they have been collectively called phytoestrogens (PE), in addition to two other classes of natural E-like substances, coumestans and lignans (13).

Currently many researchers have focused their attention on these compounds because of their protective effects against some hormone-dependent cancers (such as breast and prostate cancers) and cardiovascular disease in Asiatic

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populations, which has been suggested by numerous epidemiological and experimental studies (13–15), and also for the possible role of these compounds in the treatment of postmenopausal symptoms (16, 17). These studies have shown that the pharmacology of phytoestrogens is more complex of that of E, showing effects that can even be in opposition to their action (behaving as selective ER modulators), and activating different metabolic pathways (i.e., nongenomic actions and enzymes modulations) (2, 18). At present, the action of phytoestrogens on target organs are still under investigation. Isoflavones have been found to exert both estrogenic and antiestrogenic effects on the CNS. These effects include actions on learning and anxiety and actions on the hypothalamopituitary axis (19, 20). It is therefore possible that the isoflavone supplementation may have significant effects on brain and behavior.

In the present trial on postmenopausal women we investigated the effect of the administration of 60 mg/day of isoflavones as aglycone on cognitive function and mood.

MATERIALS AND METHODS

This randomized, double blinded, cross-over study was approved by the local Ethic Committee. All patients signed a written informed consent before being enrolled. Eighty-three postmenopausal healthy women recruited in our centers were asked to participate in this study. The women underwent a medical and psychological screening that included complete medical history and physical examination.

Inclusion criteria were: intact uterus, absence of menses for at least 12 months, FSH >30 IU/L, E₂ <10 pg/mL, and body weight range within 20% of their normal weight. Exclusion criteria were: use of medication containing E, progestins, or androgens within 8 weeks from the start of the study, presence or history of endocrinologic disorders, presence of major depression (as defined and diagnosed by standard instruments) (21), and any current illness or recent use of psychoactive medication.

After the screening, a total of 78 women were enrolled in the study.

Treatment Protocol

The 78 enrolled patients were randomly distributed in two groups (n = 39 patients in each group). The characteristics of the two groups resulted similar as shown in Table 1. Patients were treated with phytoestrogens tablets (600-mg tablets containing 60 mg of isoflavones as aglycone per tablets; 1 tablet/day) for 6 months or identical appearing placebo tablets for 6 months. At the end of the treatment there was a washout period of 1 month. After the washout period, the patients who had been treated with phytoestrogens received placebo tablets for 6 months, and those who had previously received placebo were administered phytoestrogens tablets for 6 months.

The formulated percentages in isoflavones of the phy-

toestrogens tablets were: 40%–45% in genistein, 40%–45% in diadzein, and 10%–20% in glycitein. The isoflavones used were in aglycone form. The aglycone form presents an advantage in comparison with the glucoside form; it permits the initial hydrolysis of the sugar moiety by intestinal β-glucosidases, making the compounds easily absorbable and consequently more bioavailable (13).

After the end of each treatment period, patients were administered a battery of tests. The patients and the investigators, who analyzed the results of the study, were blinded to the treatments. The results obtained from the tests after the administration of placebo in both groups were compared to those obtained after phytoestrogen treatment. Finally, we asked the patients to record the number of hot flashes experienced daily.

Psychological Evaluation

The psychological evaluation was performed according to the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV) (21). All symptoms were recorded according to the Structured Clinical Interview of the DSM-IV for assessment of nonpsychotic disorders (22). The following three standard tests were used to assess the cognitive functioning: the Digit Symbol Test (23), the Digit Span Test of the Wechsler Adult Intelligence Scale (WAIS) (23), and the Visual Scanning Test (24).

In the Digit Symbol Test, a key is provided that pairs each of the numbers 1 through 9 with a nonsense symbol. Below are rows of pairs of squares, the upper of which contains a number, the lower of which is blank. With the key available, the subject is allowed 90 seconds to complete each pair of squares by entering the appropriate symbol. The raw score is the number of correct entries completed in 90 seconds or until completion of the third row, depending on the one that occurs first.

TABLE 1

Characteristics of participants at baseline.

Characteristic	Group A (n = 39)	Group B (n = 39)
Age at start of treatment (y)	49 ± 4.3	50 ± 3.9
Height (cm)	165.5 ± 5.3	163.4 ± 5.6
Weight (kg)	67 ± 10.2	65.8 ± 10.7
Mean age at menopause (y)	50.2 ± 6.5	49.8 ± 6.3
Years of menopause	5.6 ± 4.3	5.8 ± 4.5
Parity (n)	2.8 ± 1.8	2.7 ± 1.7

Note: Values are mean ± SD. The P value for all data was not significant.

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The Digit Symbol Test measures the psychomotor performance. With the key unavailable, the subject is then requested to recall which symbol matched each number. The number of pairs correctly recalled is a measure of incidental learning. Then the subject copies 70 symbols. The less time is required for completion, the greater the subject's psychomotor speed.

The Digit Span Test is composed of two parts. In the first part patients are required to repeat spoken numbers with increasing numbers of digits to measure the immediate auditory attention. In the second part, the subjects are required to repeat the numbers in a reverse order to measure mental flexibility.

The Visual Scanning Test is used to assess the distractibility and the visual inattentiveness. The subject is shown a "target" symbol; subsequently he is given a paper with a matrix of symbols containing 60 different targets. The pa-

tient circles all the target symbols that he or she can find. The final score is obtained measuring the time needed to complete the test, omissions and errors.

The 21-item Hamilton Rating Scale for Depression (long version) (25) was used to assess the severity of depressive symptoms. A total score of 20 or more was associated with clinically important depression. Three different scales were used: the Beck Depression Inventory (BDI) (26), the Spielberger State-Trait Anxiety Inventory (27), and the Profile of Mood States (28). The BDI is a self-rating scale of 21 items, where a score of 10 or less indicates a normal mood variation and a score of 11 or more reflects increasing degrees of depression. The Spielberger State-Trait Anxiety Inventory form X1 (state anxiety) is a self-rating scale consisting of 20 items, where scores below 50 assess normality. The Profile of Mood States identifies and assesses transient, fluctuating affective mood states. The subject rates 65 items, each pertaining to an

TABLE 2

Results of the administration of the tests on cognitive performance and mood at the end of each treatment period.^a

Test/scale	Placebo (n = 77)	Phytoestrogens (n = 77)	P value ^b	Normal value
Cognitive performance				
Digit Symbol Text				
Pairs recalled correctly	6.2 ± 2.2	6.5 ± 2.4	.04	>6
Time (sec)	62 ± 17	59 ± 15	.08	—
Raw scores	51 ± 15	50 ± 14	.73	>43
Digit Span test				
Backward recall of digits	5.4 ± 1.4	5.9 ± 1.6	.05	>5
Forward recall of digits	6.5 ± 1.7	6.5 ± 1.8	.98	>5
Visual Scanning Test				
Time (sec)	81 ± 18	76 ± 17	.12	<120
Total correct	59 ± 3	60 ± 2	.60	>56
Errors	2.1 ± 1.7	1.9 ± 1.8	.56	<3
Mood scores				
Beck Depression Inventory	9.7 ± 6.9	7.6 ± 5.2	.01	<11
Spielberg State-Trait Anxiety Inventory	46 ± 9	45 ± 12	.40	<50
Profile of Mood States				
Global score	41 ± 25	34 ± 21	.01	
Fatigue—inertia	10.1 ± 4.2	7.8 ± 3.7	.001	<18
Depression—dejection	15.3 ± 8.0	10.2 ± 7.8	.001	<26
Anger—hostility	8.9 ± 6.1	7.6 ± 4.9	.04	<17
Confusion—bewilderment	6.1 ± 5.1	5.3 ± 4.3	.13	<17
Tension—anxiety	9.2 ± 4.9	8.5 ± 5.1	.27	<21
Vigor—activity	12.4 ± 3.9	13.1 ± 3.9	.31	>9

Note: Values are mean ± SD.

^a Among the 17 tests, patients had better results after treatment with phytoestrogens on 14; 6 of these differences were significant ($P < .05$). On two tests, performance was better after placebo: neither difference was significant. Forward recall of digits was essentially the same after both treatment.

^b Calculated by *t*-tests for paired data.

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aspect of a subjective state, on a scale ranging from 0 to 4. When the scores for combinations of items are added, the values of six aspects of mood and a global score are obtained.

Eight visual analogue scales provided more detailed ratings of mood by the patients. Each scale consisted of a pair of phrases, such as “as sad as possible” and “as happy as possible,” at either end of a 100-mm line. The patient places a mark at the point best corresponding to her state at that time. Measurement of the marks from the beginning of the line generated a score. At the end of the study, each patient was asked which treatment (the first or the second) was preferred.

Statistical Analysis

Data from the two treatment periods were compared by *t*-tests for paired data. Results concerning treatment preferences were evaluated by means of the McNemar’s test.

RESULTS

Of the 78 women enrolled in the study only 2 did not finish the treatment (1 in group A and 1 in group B). The first woman dropped out during treatment with placebo for personal reasons. The other woman dropped out 2 weeks after the beginning of the administration of phytoestrogens tablets for the occurrence of a moderate gastralgia.

The results of the tests pertaining to cognitive functioning and mood were all within normal limits (Table 2). Among the 17 comparisons, 6 pairs showed an advantage ($P < .05$) for the treatment with phytoestrogen and none for treatment with placebo. The performance after phytoestrogens treatment was significantly better ($P < .05$), at least in part, on the three tests of cognitive performance (Table 2). The better incidental learning was indicated by the higher scores for recall of pairs on the Digit Symbol Test, whereas the improvement in mental flexibility and attention were evident in the higher scores for recalling digits in reverse order on the Digit Span Test.

The three self-rating mood scales were concerned with depression, anxiety, or both. After treatment with phytoestrogens, the patients tended to be less depressed, as shown by the lower scores on the BDI. Moreover, their global scores and the scores on the three subscales (fatigue–inertia, depression–dejection, and anger–hostility) of the Profile of Mood States were significantly lower than scores obtained after the treatment with placebo ($P < .05$) (Table 2), indicating an improvement in the assessed conditions.

The eight visual analogue scales pertained to mood (Table 3). Patients treated with phytoestrogens had a significantly better mood on seven of the eight mood scales ($P < .04$). Their mean visual analogue scores were closer to “no symptoms” than to “severe symptoms.”

Finally, the comparison of the data concerning vasomotor symptoms showed no statistically significant difference be-

tween the two groups, although there was a slight tendency to improvement in the group treated with isoflavones (data not shown).

At the end of the study period, the patients were asked whether they preferred the first or second treatment. The results were: 49 patients preferred phytoestrogen, 9 preferred placebo, and 18 had no preference ($P = .01$). Moreover, the order of the treatment was unrelated to preference.

DISCUSSION

Cognitive impairment and depressive symptoms are two of the most common conditions affecting the elderly (29). With the rapid increase of life expectancy during the past century, these disorders are becoming widespread and current research is aiming to understand the mechanisms underlying the development of cognitive dysfunctions to prevent the occurrence of this untreatable disease, as well as preventing the eventuality of mood disturbances with the aim of improving the well-being of the aging population (30).

The CNS is one of the target tissues of E, which act both through genomic mechanisms, modulating the synthesis, release, and metabolism of many neuropeptides and neurotransmitters, and through nongenomic mechanisms, influencing enzymes activity, electrical excitability, synaptic function, morphological features, and protecting neurons from damage by free radicals and excitotoxins (1, 30, 31). The considerable data, which has been published during the past two decades concerning the localization of ERs and the molecular actions of E in the brain, has provided new knowledge about the effects and mechanisms of action of E on the CNS, together with a confirmation that these hormones may affect and regulate brain function influencing cognition and

TABLE 3
Results of the administration of the visual-analogue scales at the end of each treatment period.^a

Mood scale	Placebo (n = 77)	Phytoestrogens (n = 77)	P value ^b
Sad	45 ± 26	23 ± 27	< .001
Confused	39 ± 18	22 ± 28	< .003
Fearful	29 ± 29	20 ± 24	< .001
Irritable	40 ± 28	29 ± 26	< .002
Tense	40 ± 19	25 ± 26	< .006
Angry	34 ± 27	26 ± 21	< .01
Tired	48 ± 24	38 ± 19	< .03
Agitated	40 ± 29	36 ± 26	< .20

Note: Values are means ± SD
^a Lower score: a more favorable state.
^b Calculated by *t*-test for paired data

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mood (1, 2, 7, 30, 32). The available evidence suggesting that E are strongly implicated in the regulation of mood and cognitive functioning, as well as in their pathobiology, is far from the aim of this study and has already been extensively illustrated (1, 3, 30, 32–34).

Conjointly, in the past years many clinical trials have been performed both in women and men of different ages and conditions to assess the influence of E on mood or cognitive function and their interactions with the CNS and endocrine system. Evidence has been found on the benefits of E on cognitive functioning and also in preventing the onset of dementia/improving the symptoms in the established condition (35), together with considerable support for the psychotherapeutic benefits of E in the triad of hormone-responsive depressive disorders: postpartum depression, premenstrual depression, and perimenopausal depression (36–38). Estrogens have been shown to potentiate the effects of some antidepressants. Therefore, menopausal women with major depressive disorders may respond to lower doses of antidepressant medications when E replacement is added to the treatment regimen (39).

At present, although many clinical studies have been performed to assess the influence of E on mood or cognitive function and many investigators agree in attributing to these hormones a role of paramount importance, other researchers have not come to the same conclusions (10, 11). Numerous reasons have been offered and discussed to explain these discrepancies (34, 40, 41), including the design of the study, patients selection, the inclusion of women with a range of mood disturbances, the time the hormonal therapy begins with reference to the time of the onset of menopause (40–42), the duration of the treatment, the association of progestogens to estrogenic treatment, and the cognitive or the psychological tests used. Moreover, recent evidence from rodent, nonhuman primates, and human studies consistently suggests that there may be a critical window for the initiation of E treatment soon after the occurrence of menopause, after which HT has little or no beneficial effect on cognition (8, 41, 42).

In recent years great attention has been posed on phytoestrogens, naturally occurring compounds present in fruits, vegetables, and whole grains commonly consumed by humans. First, in epidemiological studies phytoestrogens have been found to exert beneficial effects on breast and prostate cancers. Second, due to their ability to bind ERs and behave as weak agonist/antagonist in both animals and humans, they are currently under extensive investigation for their possible role as alternative therapy for perimenopausal women. The search for alternative therapies in menopause has become an issue of great interest since the recent questioning of the long-term safety of HT (10, 11) and the evidence that lower doses of E/the use of substances with lower affinities for ERs than E₂ could be of help in reducing menopausal symptoms without increasing adverse effects (12, 43, 44). Studies have been undertaken to determine the molecular action of these compounds

at the CNS level as well as to investigate the effect of phytoestrogens on neurobehavioral functions (19, 20, 45–47).

The studies made evident that the pharmacology of phytoestrogens does not completely overlap that of E (2). This means that phytoestrogens may exhibit actions different from those of E, that may possibly add further advantage to the therapy. For example, it has been proved that phytoestrogens alter adrenocortical function suppressing glucocorticoid and stimulating androgen production *in vitro* (48). In postmenopausal women E₂ continues to be formed from circulating C(19) steroids, precursors in a number of extragonadal sites including sites in the brain. In these areas of formation, local E₂ levels can be quite high. Therefore, the circulating levels of these androgenic steroids may be important in the maintenance of local E synthesis in the brain (49).

Phytoestrogens bind both the ERs with typically different affinity and may act both as an agonist or an antagonist on the receptor they bind. As a consequence there is the possibility of more complex and diversified patterns of interaction at the tissue level, and of different therapeutic implications (50). The neuroprotective and antiapoptotic effects of some phytoestrogens, both mediated through ERs and other metabolic pathways (rapid nongenomic actions through the activation of membrane receptors) have also been assessed, compared to those of endogenous E and found to be different (2, 51). We have studied the effects of phytoestrogens on mood and cognitive function in 78 postmenopausal women (absence of menses for at least 12 months and FSH levels 30 IU/L, E₂ <10 pg/mL). As the link between mood and cognitive function has been strongly emphasized, we have assessed both aspects with the battery of tests administered to the patients.

With regard to the tests on cognitive performance and self-rating scales for mood, scores were all in the normal range after both treatments (Table 2), but on six of the tests or scales the women performed or felt significantly better after receiving phytoestrogens. These results were reinforced by the scores obtained on the visual analogue scales (where an improvement was recorded in seven of the eight scales after treatment with phytoestrogens). On the contrary, after the treatment with placebo, none of the test results improved. These data strongly suggest that the treatment with phytoestrogens may ameliorate the quality of life for most postmenopausal patients, in terms of mood and cognitive function improvement.

In conclusion, the role of E in protecting women from cognitive decline and reducing depressive symptoms has been extensively studied. Notwithstanding the conflicting results from the clinical trials performed to assess the therapeutic action of E in lowering the neurodegenerative effects of postmenopause and the onset of depressive mood, the widespread presence of ERs in the regions of the brain involved in the regulation of those functions, together with the cognition of the multiple enzymatic activity of E affecting the related metabolic pathways, seems to strongly sup-

port that these hormones should have a key role both in cognitive functioning and mood. In this study the administration to postmenopausal women of 60 mg of phytoestrogens, naturally occurring compounds indicated as possible therapeutic alternative to synthetic estrogens, for 6 months, demonstrated a positive effect on cognitive function and mood, as assessed by the appropriate battery of tests administered. This finding adds further insight to the physiological and clinical features of phytoestrogens actions, suggesting also a possible role for these compounds in relieving the psychological disturbances often associated with the complex symptomatology of menopause. (14)

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