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Spanish Menopause Society position statement: use of tibolone in postmenopausal women

Nicolás Mendoza, MD, PhD,[1] Pedro Abad, MD, PhD,[2] Francesc Baró, MD, PhD,[3] Ma Jesús Cancelo, MD, PhD,[4] Plácido Llaneza, MD, PhD,[5] Montserrat Manubens, MD, PhD,[6] Francisco Quereda, MD, PhD,[7] and Rafael Sánchez-Borrego, MD, PhD[8]

Abstract

Tibolone is a drug with complex tissue-specific action that exhibits a combination of estrogenic, progestogenic, and slight androgenic activity. Its variable profile explains its clinical effects, depending on the target tissue where it is metabolized, its metabolites' affinity for and potency in hormone receptors, and probable enzymatic activity modulation. In recent reviews and clinical trials, the effectiveness of tibolone in alleviating different hot flush menopause symptoms, mainly in mood and sexuality disorders, has been noted. In Spain, tibolone is the most prescribed hormonal treatment, and one of the most common complaints among postmenopausal women is change in sexual drive. For such reason, a panel of experts from the Spanish Menopause Society met to develop usage recommendations based on the best evidence available.

Key Words: Tibolone – Postmenopausal – Hormone therapy.

Tibolone was initially developed for the treatment of osteoporosis, but its benefits have been recognized to be extended to other organs and systems, such that this drug is currently approved for the treatment of postmenopausal women in more than 70 countries. Although the effectiveness of tibolone in alleviating hot flushes seems similar to that of low-dose hormone therapy (HT), its specific pharmacological profile adds some advantage over other HTs in women with other symptoms.

Tibolone is a synthetic molecule derived from the basic nucleus of cyclopentanoperhydrophenanthrene, with a structure related to gestagen norethynodrel. The unique configuration of this drug determines its pharmacokinetics, which, in addition to its physicochemical characteristics, permits its oral administration as a single daily dose. After being absorbed, tibolone is metabolized differently in various target tissues, yielding diverse acting metabolites, primarily 3α-OH-tibolone, 3β-OH-tibolone, and the isomer Δ^4 (the latter in the endometrium). These metabolites interact and variably potentiate estrogen, progesterone, and androgen receptors, as shown in Table 1, leading to its recognition as a selective tissue estrogenic activity regulator.[1] Furthermore, in vitro studies and other enzymatic activities have suggested that tibolone could prevent cellular proliferation, which could be of specific importance in breast tissue.[2]

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From the [1]Department of Obstetrics and Gynecology, University of Granada, Granada, Spain; [2]Hospital Torrecardenas, Almería, Spain; [3]Hospital Vall d'Hebron, University of Barcelona, Barcelona, Spain; [4]Hospital de Guadalajara, University of Alcalá, Guadalajara, Spain; [5]Asturias Central University Hospital, University of Oviedo, Oviedo, Spain; [6]Instituto Dexeus, Barcelona, Spain; [7]Hospital San Juan, Alicante, Universidad Miguel Hernández, Alicante, Spain; and [8]Clínica Diatros, Barcelona, Spain.

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Address correspondence to: Nicolas Mendoza, MD, PhD, Maestro Montero, 21, 18004 Granada, Spain. E-mail: nicomendoza@telefonica.net

EFFECTIVENESS

Vasomotor symptoms

The effectiveness of tibolone in alleviating vasomotor disorders has been compared with that of low-dose HT; as such, a recent review places this drug behind conventional HT in the reduction of the frequency of hot flushes. Compared with placebo, tibolone was more effective in relieving the frequency of vasomotor symptoms (two randomized clinical trials [RCTs], n = 847; odds ratio, 0.42; 95% CI, 0.25-0.69), although only tibolone 2.5 mg/day was significantly better than placebo. Compared with HT, tibolone was less effective in relieving the frequency of vasomotor symptoms (two RCTs, n = 545; odds ratio, 4.16; 95% CI, 1.50-11.58).[3]

In most clinical trials supporting this meta-analysis, it is striking that no significant differences in the improvement of these symptoms have been found between tibolone and HT. In another review from 2010, no differences were observed between conventional HT and tibolone.[4]

Data from a recent RCT confirmed that tibolone is significantly more effective than placebo and as effective as low-dose continuous-combined estradiol (E_2)/norethisterone acetate (NETA) in reducing vasomotor symptoms.[5,6] An RCT of

TABLE 1. *Affinities of tibolone and its metabolites for steroid receptors*

Steroid	Steroid receptor		
	Estrogen	Progesterone	Androgen
Tibolone	Weak	Weak	Weak
Isomer Δ^4	None	Moderate	Moderate
3α-OH–derived	Weak	None	None
3β-OH–derived	Weak	None	None

two doses of tibolone (1.25 and 2.5 mg) for the treatment of moderate to severe vasomotor symptoms and of symptoms associated with vaginal atrophy confirmed the usefulness even of low doses. This RCT also found that both doses of tibolone significantly reduced the severity of flushes at 12 weeks (mean changes in severity scores: −1.7 with tibolone 2.5 mg vs −0.9 with tibolone 1.25 mg vs −0.3 with placebo; $P < 0.001$ for both tibolone 2.5 mg and tibolone 1.25 mg vs placebo).[7]

In a review of our data (some included in the review of Mendoza et al[8,9]) on women with moderate to severe vasomotor symptoms, tibolone was as good as estrogen therapy (93.1% vs 96.1%).

Quality of life

Not only does it seem that tibolone is not inferior to conventional HT in the improvement of menopausal symptoms, but there are findings suggesting that global positive effects could be greater with tibolone, especially on nonvasomotor menopausal symptoms. An RCT that compared tibolone, 17β-estradiol, and placebo in a group of women with surgical menopause found differences in favor of tibolone in the alleviation of symptoms other than vasomotor symptoms (including nervousness, sleep disturbances, difficulty concentrating, sensation of fatigue or loss of energy, disinterest, crying, and migraines).[10]

In our study, tibolone was better than estrogen therapy in alleviating mood and sexuality disorders, but it did not reach statistical significance (76.5% vs 42.8%, $P = 0.08$; and 91% vs 47%, $P = 0.056$, respectively).[9]

One possible explanation for these findings is that tibolone normalizes β-endorphin levels, behavioral changes, and mood disorders caused by the combined activity of its metabolites on the central nervous system: that of the isomer Δ^4 binding with receptors for androgens and those of the derived 3α-hydroxy and 3β-hydroxy forms binding with receptors for estrogens.

Precisely because there are symptoms other than hot flushes that impact quality of life and because the presentation of climacteric syndrome is influenced by notable biological and cultural aspects, a group of experts from Oceania and East Asia has presented a position on the use of tibolone, arguing that this medication is a treatment that offers additional possibilities to those offered by conventional HT; this position came from a geographic area where the main medical consultations were related to insomnia.[6] Along these lines, the international consensus of 2005 compares tibolone with conventional HT in effectiveness against vasomotor symptoms, but the former is given a superior position in the overall improvement of quality of life. This document points out the action of tibolone against sleep, sexuality, and mood disorders; combined with the fact that bleeding is scarce and breast discomfort is lesser with tibolone, these findings indicate that tibolone may be the treatment of choice for women who present with mood changes, apart from vasomotor symptoms and musculoskeletal pain.[5]

Although scarcity of bleeding with tibolone has been suggested as one of the factors that contribute to its users feeling better than those who take conventional HT (bleeding with tibolone: 18.3% vs 33.1% at 1-3 mo, $P < 0.001$; and 11% vs 19% at 7-9 mo, $P < 0.05$, with respect to transdermal E_2/NETA), there are symptoms other than hot flushes that affect quality of life and could be better alleviated by tibolone, probably mediated by its slight androgenic effect.[11]

Sexuality

Tibolone reduces vaginal dryness and symptoms resulting from this condition (dyspareunia, pain, itching, or vaginal lubrication) similarly to conventional HT.[11] In addition, tibolone has a positive effect on other aspects of sexuality, making it comparable to the combination of HT with androgens (Table 2).[12]

Admittedly, the beneficial effects of therapies aiming to improve feminine sexuality are modest, and RCTs of tibolone compared with testosterone have not been performed. Instead, RCTs that use specific scales for evaluating sexuality—primarily the Female Sexual Function Index scale—demonstrate overall improvement for any HT versus placebo but offer better outcomes for tibolone within specific parameters such as desire, orgasms, frequency of intercourse, responsiveness, arousal, or satisfaction.[13-16]

In the Livial International Study in sexual Arousal disorders (LISA), which is the main RCT conducted on sexuality with tibolone, the total Female Sexual Function Index score and the subscores for arousal, desire, and satisfaction showed a significant increase from baseline ($P < 0.001$) for both tibolone and E_2/NETA (32% vs 26% per protocol analysis, $P = 0.025$ between groups).[13]

Tibolone has a significantly better tolerability profile than transdermal E_2/NETA, as measured by vaginal bleeding, breast pain, and treatment continuation: bleeding/spotting events (16% vs 56% at weeks 1-12, $P < 0.001$; 12% vs 51% at

TABLE 2. *Aspects of sexuality in which improvement has been observed with tibolone*

Relative to a placebo:
• Increase in blood flow and vaginal lubrication
• Increase in sexual fantasies, sexual desire, and arousal
• No differences in intercourse frequency, sexual activity without penetration, or initiation or rejection of sexual activity
• Increase in plasma testosterone and sex hormone–binding globulin
Relative to hormone therapy:
• Increase in desire, orgasms, intercourse frequency, responsiveness, arousal, or satisfaction
• Increase in plasma testosterone and decrease in sex hormone–binding globulin

weeks 13 and 24, $P < 0.001$), vaginal hemorrhage (11% vs 0%, $P < 0.001$), and breast signs and symptoms (11% vs 4%, $P = 0.015$).[17]

Cardiovascular effects

Tibolone exhibits heterogeneous action on lipid profile but generally has properties that could be considered antiatherogenic. Although tibolone reduces high-density lipoprotein cholesterol, the most important of its lipid effects, in contrast to estrogen, is a marked reduction in triglycerides, which constitute an independent risk factor for insulin resistance and cardiovascular disease.[18]

In addition to these lipid-based mechanisms, several actions of tibolone for cardiovascular protection have been proposed. This drug reduces the concentration of lipoprotein(a), an agent that is both atherogenic and thrombotic[19]; in addition, it does not modify the levels of C-reactive protein.[20] Its endothelial activity is similar to that of estrogen: in experimental animal studies, a reduction in the progression of atherogenic plaques and endothelial damage, independent of lipid plasma levels and probably mediated by nitric oxide, was observed.[21-23]

Regarding carbohydrate metabolism, in women with and without diabetes mellitus, it has been observed that tibolone does not change the blood levels of glucose, insulin, C-peptide, or glycosylated hemoglobin, nor does it induce changes in oral glucose tolerance.[24]

However, the Long-term Intervention on Fracture with Tibolone (LIFT) study, a trial directed at evaluating the ability to prevent fractures, had to be stopped early due to the increased risk of stroke in women treated with tibolone (relative hazard, 2.19; 95% CI, 1.14-4.23; $P = 0.02$). Nevertheless, these women did not present an increased risk of coronary heart disease or venous thromboembolism (VTE). Perhaps age could be a determining factor in this finding, as the average age of women exceeded 68 years. Although the differences in absolute risk between groups did not reach statistical significance and a greater thrombotic or coronary risk was not recognized, the authors do not recommend beginning treatment with tibolone in women older than 60 years who present an increased risk for stroke.[25]

The Osteoporosis Prevention and Arterial effects of tiboLone (OPAL) trial reported that both tibolone and the combination of conjugated equine estrogens (CEE) and medroxyprogesterone acetate (MPA) were associated with the progression of carotid intima-media thickness compared with placebo. The differences from placebo (0.0042 mm/y for tibolone and 0.0039 mm/y for CEE/MPA) were statistically significant ($P = 0.03$ and $P = 0.04$, respectively). However, this interpretation is questionable owing to inexplicable differences in results between the European women and the American women in the trial.[26] Subsequent comments on the trial reported that OPAL shows that neither tibolone nor CEE/MPA has beneficial effects on atherosclerosis, but neither were they harmful.[18]

In an RCT with placebo in a group of 100 healthy postmenopausal women younger than 65 years, tibolone did not affect the resistance of small-caliber cerebral arteries.[27]

Finally, in other cohort studies or in RCTs in which the objective was not the consideration of cardiovascular events, no more myocardial infarction or stroke was observed with tibolone, perhaps because the age of the women studied was closer to the age at natural menopause.[28]

Skeletal effects

Tibolone produces a direct agonistic effect on estrogen receptor, leading to increased bone mineral density (BMD), reduction of the biochemical markers of bone resorption to premenopausal values, and reduced risk of vertebral and nonvertebral fractures. The lumbar spine BMD increase described at around 2 years of tibolone treatment varies between 3.8% and 12%. In the Study of Tibolone's Effects on osteoPenia (STEP), significant increases in BMD were observed versus raloxifene (3.8% vs 2.1% in the lumbar spine, $P < 0.001$; 1.26% vs 0.44% in the hip, $P < 0.005$).[29]

In the LIFT study, tibolone reduced the risk of both vertebral and nonvertebral fractures compared with placebo (43% and 26%, respectively).[20] The risk reduction of vertebral and nonvertebral fractures was 8.6 and 6.9 per 1,000 patients/year, respectively (relative risk [RR], 0.55; 95% CI, 0.41-0.74; $P < 0.001$; and RR, 0.74; 95% CI, 0.58-0.93; $P = 0.001$, respectively). These benefits have been noted in postmenopausal women of any age, independent of whether menopause was natural or surgical, and even in women with a history of breast cancer.[30-32]

SAFETY

Although a recent review suggests that tibolone may not be a good choice for long-term use, especially in women older than 65 years, available data on the long-term safety of tibolone are satisfactory, specifically when tibolone is used in healthy early postmenopausal women with no personal history of breast cancer.[33]

Endometrium

Tibolone does not produce an estrogenic effect on the endometrium owing to the local metabolism of the isomer Δ^4, which stimulates progesterone receptors. Thus, it decreases bleeding, and risks of endometrial hyperplasia and adenocarcinoma in clinical trials were similar to those with placebo.[34]

In general, bleeding with tibolone is not very frequent and typically presents in young women during the first 3 months of treatment, when endogenous estrogen is still secreted. As previous studies have described, in cases of polyps, fibroids, or atrophy in bleeding, acting in the same manner by which abnormal uterine bleeding would be managed is recommended.[35-37]

In the Million Women Study, an increase in endometrial cancers was described in women treated with tibolone. Besides the widely criticized shortcomings in the design of this study, it should be noted that women treated with tibolone had previously received estrogen treatment without gestagenic opposition, which placed them at an increased risk for endometrial adenocarcinoma before the start of tibolone use.[38]

In the Tibolone Histology of the Endometrium and Breast Endpoint Study (THEBES), which is an RCT on endometrial safety with tibolone and CEE/MPA in 3,224 women, those treated with tibolone did not present endometrial cancer or hyperplasia, and ultrasonographic endometrial thickness was not greater than that in the CEE/MPA group, additionally indicating better tolerance of tibolone compared with women treated with CEE/MPA.[28]

These results are consistent with those of the OPAL study, the secondary objective of which was to measure endometrial safety without recording greater endometrial pathology versus placebo.[26]

Breast

In experimental animal studies or in vitro culture studies, tibolone has shown an ability to inhibit the conversion of estrone into E_2 in breast tissue and the appearance of chemically induced tumors, to reduce the rate of proliferation, and to increase the differentiation of epithelial mammary cells, increasing apoptosis phenomena.[39]

Moreover, the breast pain/tenderness observed in women treated with tibolone has been lower than that in women treated with other HTs (3.2% vs 9.8% with transdermal E_2/NETA, $P < 0.001$).[11] These results are similar to the result described in THEBES—less breast pain in the tibolone group than in the CEE/MPA group (4.3% vs 12.7%, $P < 0.001$).[28]

Some observational studies have reported that tibolone does not increase mammographic density.[40,41] Although an increased risk of breast cancer was recorded among tibolone users (RR, 1.45; 95% CI, 1.25-1.68; $P < 0.0001$) in the Million Women Study, this finding has not been verified in other series.[42] On the contrary, in the LIFT study, a decrease in the risk of breast cancer was observed in the group treated with tibolone in comparison with the placebo group (relative hazard, 0.32; 95% CI, 0.13-0.80; $P = 0.02$).[20]

Owing to generally positive results observed in the breast,[43] the Livial Intervention following Breast cancer; Efficacy, Recurrence, And Tolerability Endpoints (LIBERATE) study was designed to compare the effectiveness and safety of tibolone against placebo in the treatment of vasomotor symptoms among 3,148 women who had overcome the disease. After an average follow-up of 3 years, 237 (15%) of 1,156 women using tibolone experienced a recurrence of breast cancer, in comparison with 138 (11.4%) of 1,213 women in the placebo group (hazard ratio, 1.40; 95% CI, 1.1-1.79); for this, the study was halted 6 months before the planned date.[44]

Consequently, although tibolone alleviates vasomotor symptoms and improves BMD, the use of this medication is not recommended for women with a history of breast cancer.

Other cancers

There was no evidence that tibolone had detrimental effects on the progression, free survival, and overall survival of patients with epithelial ovarian cancer.[45]

In the LIFT study, a decreased risk of colon cancer with tibolone, compared with placebo, was observed (relative hazard, 0.31; 95% CI, 0.10-0.96; $P = 0.04$).[20]

Hemostasis

Strictly speaking, research on the parameters implied in hemostasis is still unclear, but most investigations examining the effects of tibolone agree that this drug does not increase the risk of thrombosis.

A significant decline in fibrinogen and factor VIIa and a rise in D-dimer and fibrin degradation products were detected after 24 weeks of tibolone treatment.[46] Moreover, a higher activated protein C resistance ratio observed in women undergoing tibolone treatment[47] may translate into a corresponding low risk of deep vein thrombosis, as is also indicated by existing clinical data.[48-50]

However, the LIFT study had to be halted when an increase in stroke was observed in women undergoing treatment with tibolone. If we accept that the procoagulant effect of oral HT is related to the first-pass liver metabolism of the estrogenic component, tibolone could be predicted to act this way. However, its hemostatic effects are more androgenic than estrogenic. Moreover, in the LIFT study, not a single thrombotic or coronary event was recorded, and it has been suggested that the increase in stroke could be related to the age of the women (mean age, 68 y) or to the presence of other risk factors (smoking, hypertension, etc).[20]

Studies subsequent to the LIFT study that have compared the hemostatic changes occurring in women taking conventional HT, tibolone, or raloxifene show that women treated with tibolone exhibit a pronounced decline in factor VII, a smaller reduction in antithrombin and protein C, and even an increase in other coagulation inhibitors.[51,52]

Consequently, the new research seems to corroborate the idea that tibolone behaves hemostatically differently from oral HT, with its slight androgenic properties predominating such that its use has not been associated with an increase in the risk of deep vein thrombosis in postmenopausal women.

Tibolone is a valuable and safe treatment option for healthy early postmenopausal women with climacteric complaints and might be preferable to conventional HT for women with surgical menopause and for those with intact uterus. However, in women older than 65 years or in patients with breast cancer, available data on the safety of tibolone are of concern owing to the increased risk of stroke in a separate RCT and the recurrence of breast cancer, respectively.

DISCUSSION

There are several reasons for elaborating a position on tibolone in Spain: (1) this medicine has been the most widely used HT for two decades; (2) it continues to be widely prescribed; and (3) it has suffered the least decrease in sales after the publication of the Women's Health Initiative study.[53,54]

Although the effectiveness of tibolone has been equated with that of low-dose HT, its unique pharmacological profile gives it some advantage over any of the HTs available for women with symptoms other than hot flushes. The advantages of tibolone over conventional HTs stated in the latest guidelines of the International Menopause Society include a more

effective alleviation of mood disorders and female sexual disorders.[5]

In fact, in Spain, sexual disorder is one of the major concerns among postmenopausal women, making tibolone an ideal treatment.[55] The data that we use indicate that sexuality disorders are brought up in most consults of postmenopausal Spanish women—sometimes in an obvious way and many other times indirectly[12]—and that the effectiveness of tibolone could be comparable to that of the combined use of HT and androgens.[56] Sexuality is also a frequent complaint elsewhere and clearly alters quality of life, so our recommendation can be extended to other countries.[57]

Along the same lines, tibolone can treat women with surgical menopause better than conventional HT does because tibolone can alleviate the effects of the deficit of other nonestrogen hormones. In an RCT performed in Spain in which tibolone and transdermal 17β-estradiol were administered in women with surgical menopause, differences in favor of tibolone were found in the alleviation of nonvasomotor symptoms such as nervousness, sleep disturbances, difficulty concentrating, sensation of fatigue or loss of energy, disinterest, crying, and migraines. The improvement in sexuality-related symptoms was higher in women taking tibolone than in women taking placebo, with similar percentages of compliance and adverse effects.[9]

TABLE 3. *Summary of the recommendations of the Spanish Menopause Society*

Recommendation	Level of evidence
Tibolone is comparable to a low-dose HT in alleviating vasomotor symptoms.	2B
When other symptoms predominate (insomnia, nervousness, disinterest, fatigue, and loss of concentration), the specific profile of the clinical effects of tibolone can make a good option.	2C
Tibolone is indicated for women with androgenic deficit syndrome. Tibolone has shown itself to be superior to conventional HT in women with surgical menopause.	2C
Tibolone can be an alternative to conventional HT for the treatment of postmenopausal women with sexuality changes.	2B
Tibolone reduces bone turnover, increases BMD, and reduces the risk of vertebral and nonvertebral fractures.	2A
Tibolone shows beneficial effects on certain surrogate markers of cardiovascular disease, specifically in the reduction of triglycerides. The use of tibolone is not recommended for the primary or secondary prevention of cardiovascular disease.	2B
Beginning treatment with tibolone in women older than 60 y who present risk factors for stroke is not advised.	2B
Tibolone has been associated with an increased risk of venous thromboembolism less than that associated with oral HT.	2B
Tibolone seems to be safe in its action on the endometrium.	2A
Tibolone does not increase breast density or mastalgia among postmenopausal woman.	2C
The use of tibolone is not recommended for women with a history of breast cancer owing to an increased risk of recurrence.	2A

Levels of evidence: 1A, strong recommendation, evidence of high quality; 1B, strong recommendation, evidence of moderate quality; 1C, strong recommendation, evidence of low quality; 2A, weak recommendation, evidence of high quality; 2B, weak recommendation, evidence of moderate quality; 2C, weak recommendation, evidence of low quality.
HT, hormone therapy; BMD, bone mineral density.

Moreover, safety information on hemostasis is available; this will be included in the technical record for tibolone, primarily based on data extracted from a British case-control study.[58] The Spanish Agency of Medicines and Healthcare Products has issued a report showing that the risk of VTE associated with tibolone use is lower than the risk of VTE associated with oral HT use.[59] However, these data are very limited such that they do not exclude the possibility of a small risk of VTE among women taking tibolone in comparison with women not taking this medication.

Lastly, in Spain, tibolone is not indicated for the prevention of osteoporosis among asymptomatic women. However, in several other member states of the European Union, it is authorized for the prevention of osteoporosis among postmenopausal women who face the risk of fractures and who cannot tolerate the use of other antiosteoporotic medications or for whom the use of other antiosteoporotic medications is contraindicated.

CONCLUSIONS

The effectiveness of tibolone has been equated with that of low-dose HT, but its unique pharmacological profile gives it an advantage over any of the HTs available for women with mood disorders or sexual disorders (two of the major concerns among Spanish postmenopausal women), making tibolone an ideal treatment. Its effectiveness seems to be comparable to that of the combined use of HT and androgens. From the point of view of safety, the risk of VTE associated with tibolone use is lower than that associated with oral HT use.

LIST OF RECOMMENDATIONS

The Spanish Menopause Society considers it appropriate to develop its own recommendations based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system[60] to elaborate clinical practice guidelines and to classify quality of evidence and strength of recommendations (Table 3).

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