Endocrine, *vol. 24, no. 3, 231–238, August 2004* 0969–711X/04/24:231–238/$25.00

New HRT Options for the Treatment of Menopausal Symptoms and the Maintenance of Quality of Life in Postmenopausal Women

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Quality of life (QoL) is an important aspect that reflects the way people feel and function. The assessment of QoL quality of life is an essential tool for estimating the efficacy of any therapy in different pathophysiological conditions. In normal, healthy women, the perception of QoL can be significantly modified during the peri/postmenopausal period. Conventional HRT improves not only symptoms, but also QoL. Selection of patients, as well as the choice of a personalized HRT in terms of doses, types, routes of administration, and combination, are the keys to optimize the benefits and reduce the risks. One type of HRT cannot fit all populations of postmenopausal women. The safety and the benefit/risk ratios reported for the standard higher doses used in the past, as well as in the HERS and WHI trials, cannot vaguely be referred to different preparations, and particularly to newer HRT schedules with lower dosages. The demonstration of efficacy of lower-dose HRT provides important information for the treatment of the postmenopausal syndrome. Lower-dose HRT (as 0.3 mg/d of conjugated estrogens) minimizes the side effects and is likely to improve compliance to the treatment. The choice of lower estrogen doses may at least in part reduce the potential risks of postmenopausal hormone use, while maintaining the benefits of conventional HRT.

Key Words: Menopause; HRT; quality of life.

Menopause and Quality of Life

Quality of life (QoL) is an important aspect that reflects the way people feel and function. Perception of QoL in different pathophysiological conditions depends not only on consequences and clinical symptoms of health status, but also on a broad spectrum of socioeconomic conditions and personal experiences. In normal, healthy women, the perception of QoL can be significantly modified during the peri/postmenopausal period *(1–5)*. The menopause transition often brings along hot flushes and sweats, mood alterations, sleeplessness, and sexual dysfunction, the impact of which may be noteworthy on the QoL. In otherwise normal subjects, postmenopausal estrogen deficiency can be a fundamental and/or a contributing factor for different conditions and diseases that can induce a worsening of a woman's health and QoL *(1–5)*. Thus, during climacteric transition and after menopause, QoL evaluation can be considered an essential component to provide a comprehensive picture of the effect of the menopause and to assess the possible benefits of different treatments.

The main clinical effect of estrogen decline is the onset of menopausal syndrome. The onset of subjective symptoms is the major reason why perimenopausal women seek medical treatment (Fig. 1). Hot flashes is the typical sign of estrogen decrease around the time of menopause. Vasomotor symptoms (hot flushes and sweats, often associated with annoying sleep disturbances) may start much earlier and continue far longer than is commonly recognized by doctors and acknowledged in gynecology manuals. Owing to this indication, the vast majority of symptomatic women start HRT around the time of menopause (Fig. 2), while only a minority start any form of hormone supplementation after 5 yr or more from the last menstrual period. Severity may change in different women: up to 80% of women experience hot flashes, and 20–25% severely. The severity and general patterns of hot flashes may change with time since menopause. In some women hot flushes become less frequent and less intense, but in others they may continue at hourly intervals well into old age *(3)*. Hormone replacement therapy (HRT) can be used to stop or reduce climacteric symptoms and to maintain the physical and psychological day-to-day functioning of the postmenopausal woman *(6–12)*.

The QoL Measurement in Postmenopausal Women

QoL is traditionally measured with either generic or specific instruments *(5)*. Generic health status measures are broadly applicable across different conditions or diseases, various treatments or interventions, and diverse patient

Received June 22, 2004; Revised August 5, 2004; Accepted August 10, 2004.

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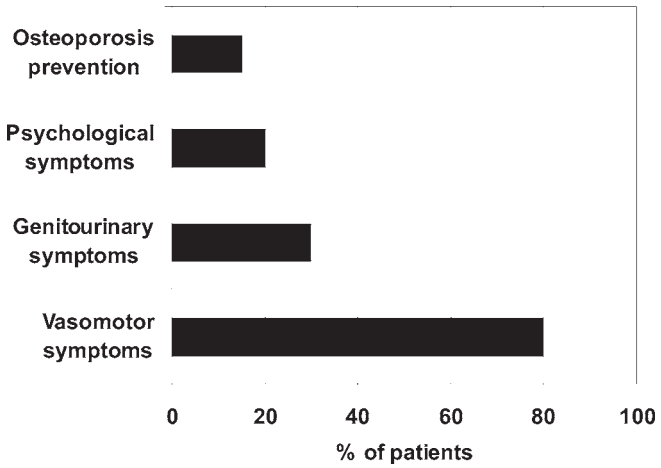

Fig. 1. The reasons to take HRT. Data report the main reason(s) to seek medical treatment in 1023 women consulting the Menopause Center at the University Hospital Santa Chiara, Pisa, Italy, in 2002. Women were reporting the reasons to seek medical treatment using a questionnaire with the possibility to indicate three different indications.

Fig. 2. This figure reports the timing of HRT initiation according to years since menopause in 1023 women consulting the Menopause Center at the University Hospital Santa Chiara, Pisa, Italy, in 2002. The results are reported as the percentage of subjects.

populations. They are intended to measure aspects of health or QoL which are common to different impairments, diseases, and patients. Disease-specific measures are designed to assess the impact of specific conditions on health status. They may be more sensitive for the detection and quantification of small changes that are important to clinicians and patients *(13–15)*. Thus, the measurement of QoL needs specific instruments that are designed to evaluate perimenopausal women.

The Women's Health Questionnaire (WHQ), a specific tool to measure QoL, has commonly been used to assess physical and emotional symptoms and sensations experienced by mid-aged women and provided important information in the evaluation of QoL improvement in response to hormone replacement therapy *(13,16,17)*. The Women's Health Questionnaire was developed in England to investigate psychological and somatic symptoms experienced by peri- and postmenopausal women. The psychometric properties of this instrument have already been well documented in a variety of populations, which have different sociocultural roots and characteristics. Psychometric properties measured by the questionnaire demonstrate that there are no major cross-cultural differences in the perception of QoL in climacteric women *(17)*. In addition, QoL of women attending menopause centers is similar to that in age-matched samples of the general population *(17)*.

Other nonspecific questionnaires such as the Short-Form Health Survey (SF-36), the most widely used generic health status measure, have been used in large population studies and in many different clinical conditions, showing excellent psychometric properties. However, when applied to the same population, the specific measure with the Women's Health Questionnaire can provide more clinically sensible information for the condition investigated, as shown by the general low correlation between SF-36 and vasomotor and menstrual symptoms scores *(17)*.

The Effects of HRT on QoL

As HRT is started in symptomatic women, QoL can be improved to a level comparable to that of premenopausal women *(11)*. It can be suggested that the effect of HRT on QoL is mediated through the effects on subjective symptoms, namely vasomotor disorders. However, there is evidence suggesting that the improvement of QoL in HRT-treated women cannot be totally ascribed to effects on vasomotor symptoms. HRT has been reported to improve psychological function in asymptomatic women *(12)*. This indicates that the beneficial effect is not merely caused by its clinical efficacy on vasomotor symptoms, as shown by its effectiveness, regardless of the presence or absence of the flushes *(12)*. On the other hand, the effects on QoL observed after short-term HRT administration (from a few weeks to some months) cannot be ascribed to relevant variations in socioeconomic or cultural status of HRT-treated women. In conclusion, a large body of evidence suggests that well-timed HRT improving climacteric symptoms can also preserve QoL of menopausal women *(6–12)*. Thus, there is a major consensus that HRT cannot only cure subjective symptoms of estrogen deficiency but also improve QoL in menopausal women.

A surprising null effect of HRT on QoL was reported by Hayes et al., from the Women's Health Initiative (WHI) *(18)*. This paper was clearly a surprise for the medical community and deserves a comment that is critical for the interpretation of all the WHI results. All the recent WHI reports regarding HRT have caused great uncertainty and alarm among physicians, women, and the media *(19,20)*. The negative or null results regarding the QoL, as well as coronary heart disease have been misinterpreted. In fact, the WHI study was conducted in a population of older (63 yr of age, mean menopausal age 12–13 yr), largely asymptomatic postmenopausal women, with a series of risk factors for cardiovascular disease (as obesity and hypertension) in a high percentage of the subjects. It is relevant to underline that in the WHI article on QoL *(18)*, the reader can find significant reductions in some of the items evaluated with the generic instrument (the SF-36). The reasons why the authors chose this generic instrument, rather than a specific questionnaire, are obscure. However, in the "Discussion" section the authors concluded that the changes induced by HRT in some QoL aspects were so small that they were clinically insignificant. However, the changes were modest starting from low baseline mean scores, because the selected population consisted of barely symptomatic elderly women. Therefore, as far as QoL is concerned, in the WHI the wrong population was measured with an inaccurate instrument.

WHI was not intended to be a study of menopause, but a study to determine whether hormones that are very effective in relieving menopausal symptoms have value in the prevention of chronic diseases in elderly women *(19,20)*. However, the null QoL results obtained in this peculiar population with a nonspecific questionnaire, as well as some other findings of the WHI study, were misinterpreted by some experts. Consequently, groups of scientists redefined guidelines on the indication of HRT. The media coverage of the negative WHI results' interpretation was huge. As a consequence, a vast proportion of HRT-treated women stopped their treatments, and a growing proportion of perimenopausal women, even suffering from serious climacteric symptoms, will not be treated. The ultimate effect will be that untreated menopausal women will be transformed into a growing population ready for potential prescriptions of alternative, expensive drugs.

HRT for Symptoms and QoL: Personalization and Selection

In the vast majority of women, practicing clinicians prescribe HRT around the time of menopause, basically for the onset of symptoms (Fig. 2) *(21)*. After the menopause, women are not completely estrogen-depleted: the extent and the clinical relevance of this deficiency and its effects on different tissues, organs, and apparatuses depend on the time since menopause, type of menopause, and body weight. Any given woman has her personal needs of hormone supplementation and personal preferences in terms of routes of administration. Different estrogen–progestogen doses and combinations should be used in different age groups and conditions specific for the women seeking medical assistance for menopause-related problems *(21–25)*.

The main lesson from WHI is that one size of HRT does not and cannot fit all the postmenopausal women. Personalization of doses and combinations are the key to guarantee the maximum benefits with the minimal risk. Different age groups, at different times since menopause, may need different HRT preparations, with progressively lower doses of hormones (Fig. 3). In perimenopausal women the choice of the correct HRT dose and the timing of treatment is relevant particularly because of the possible negative effects. Maintaining stable estrogen levels during menopausal transition, tapering the estrogen dose in the postmenopausal years, and always using the minimum effective dose are the markers of clinical management of the postmenopausal years (Fig. 3). These criteria are opposed to those used in the HERS and WHI trials where elderly postmenopausal women were treated with standard dose HRT, starting even after 15–20 yr of untreated hypoestrogenism. It is imperative to emphasize that we cannot treat women with an age varying from 50 to 79 yr, with a drug that was studied and approved for the treatment of early postmenopausal women *(22)*. If a given dose is suitable for a 50-yr-old woman, as the 0.625 mg of conjugated estrogens, this is definitely an overdose at 70–79 yr (Fig. 3). In clinical practice nobody prescribes a product specifically designed and studied for perimenopausal women *(22)* to a population of women 30 yr older *(23–25)*. Thus, randomized clinical trials have clearly demonstrated

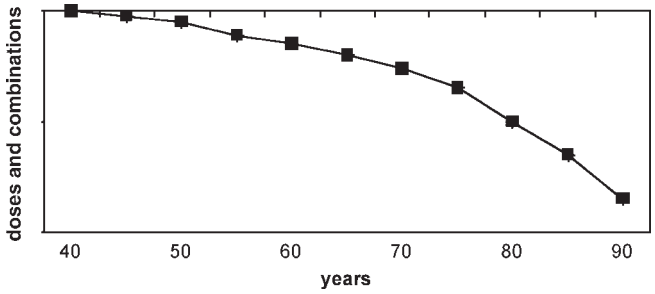

Fig. 3. HRT dose selection criteria. The choice of different HRT doses and combinations changes according to age, years since menopause, personal needs, the health profile and preferences of individual women, and the personal risk/benefit ratio.

that one type of HRT cannot fit all postmenopausal and elderly women, and this is well recognized in standard clinical practice. HRT is not a remedy that can be dispensed to everyone without proper selection (Table 1). The selection is critical, and women select themselves in attending the Menopause Clinic, around the time of menopause, usually in good health and with a prevalent subjective syndrome (Table 1). In addition, when physicians select the women to be prescribed HRT, a further selection is usually performed, excluding for example the hypertensive subjects (Table 1). In Table 1, the characteristics of women included in the QoL studies are put side by side with those of the whole population attending the menopause center at the Pisa University Hospital, and for further comparison to the characteristics of the WHI population. The remarkable difference is evident in the women included in the WHI trial and those that were selected to be treated with hormones in the QoL studies. The population treated with HRT was selected from the women attending the Menopause Center, and it is relevant to note that, for example, the hypertensive women were excluded (Table 2). Thus, the population selection is critical. The increase in cardiovascular events described during the first year or so in the WHI and HERS trials, seems to be strongly related to delayed hormone treatment and to specific characteristics of the populations in terms of age and CVD risk factors *(19)*. This so-called early arm does not exist in healthy, symptomatic postmenopausal women, aged 50–59 yr *(26)*, and the magnitude of the expected increase in deep-vein thrombosis with HRT is consistent with previous data *(27)*. An earlier initiation in symptomatic perimenopausal women can reduce the progression of atherogenesis, a later hormone intervention can only be dangerous in term of procoagulant effects in patients with atherosclerotic plaques *(27)*. These findings suggest that the results of early CHD risk observed in the HERS and WHI studies are not applicable to healthy, younger peri-postmenopausal women who seek treatment for menopausal symptoms *(23–25)*. Thus, clinicians prescribing HRT to treat symptoms in healthy, early postmenopausal women, should not be concerned about the risk of cardiovascular events. In this regard, any intervention alternative to HRT must be proven to be safe and effective, avoiding inappropriate enthusiasms with products of unproven efficacy and safety *(28)*.

Table 1
Characteristics of Different Populations[a]

	WHI EP arm (%)	Menopause Clinic, Pisa (%)	PISA QoL STUDY (HRT treated) (%)
Age (yr)	63	53	54.4
<60	33.4	86	90
60–69	45.3	10	10
70–79	21.3	4	0
BMI	28.5	24.5	24.5
<25	30.4	64	76
25–29	35.3	27	24
>30	34.2	7	0
Hypertensive	35.7	14	0

[a]In the first column the salient characteristics of the women included in the WHI trial, and in the other two columns the characteristics of women attending the Menopause Center at the Pisa University Hospital (Italy), and the women included in an HRT study.

Table 2
Baseline Characteristics
of Postmenopausal Women Participating
in the Low-Dose Conjugated Estrogens QoL Study

	Control (n = 30)	LD-HRT (n = 90)
Age (y)	52.3 ± 0.3	52.4 ± 0.5
YSM	1.5 ± 0.7	1.7 ± 0.5
BMI (kg/m^2)	24.8 ± 0.9	25.1 ± 0.5
FSH (IU/L)	75.4 ± 4.8	71.5 ± 5.5
Estradiol (pg/mL)	15.4 ± 5.3	10.2 ± 7.4

Control group = postmenopausal women receiving 1000 mg of calcium per day; LD-HRT = postmenopausal women receiving oral 0.3 mg/d of conjugated estrogens plus a low dose of different progestins. YSM = years since menopause; BMI = body mass index; FSH = follicle-stimulating hormone.

The Low-Dose HRT—Early Initiation Model

Conventional, standard doses of HRT (0.625 mg/d of oral conjugated estrogens) are known to reduce or abolish the symptoms related to estrogen deficiency. The estrogen decrease around the time of menopause does not induce the same symptoms with the same severity and duration in all climacteric women. The clinical signs of estrogen decline, namely the psychological and vasomotor symptoms, such

as hot flushes themselves, may disclose the brain's susceptibility to estrogen reduction, selecting the population that can be particularly responsive to estrogen replacement *(29)*. Estrogen has a positive effect on neurofunction, improving neurotransmission, neuroprotection, neurite branching synaptogenesis, cerebral blood flow and trophic factor expression *(29)*. Its depletion may impair memory, cognitive function, and accelerate the onset of Alzheimer's disease *(29)*. This defensive brain effect depends on how early treatment is initiated and the duration of treatment. According to the Cache County Study *(30)*, early initiation and continuation of HRT after menopause may halt degeneration and provide some cognitive protection. Conversely, no neurocognitive protection was evident when HRT was started in asymptomatic elderly women, 10–15 yr after menopause *(30,31)*. climacteric symptoms can last from a few months to several years and a sizable proportion of elderly women can suffer from estrogen-deficiency-related symptoms many years after menopause *(32)*. Although in some women hot flashes and other symptoms attributed to menopause persist for many years after the cessation of menses, and HRT reduces hot flashes, trouble sleeping, and vaginal dryness, standard doses in elderly women are associated with a high rate of side effects *(32)*. As previously reported, HRT has been prescribed at a "standard" dose of 0.625 mg/d of conjugated equine estrogens (CEE) or the equivalent. This approach was based primarily on early evidence that this is the amount required to prevent osteoporosis. Until now, women given lower doses generally have been elderly patients. Today, there is an increasing body of evidence that the use of lower doses of HRT (LD-HRT) for younger postmenopausal women achieves adequate levels of efficacy and safety. Lower estrogen doses than the gold-standard 0.625 mg/d of oral conjugated estrogens or equivalent doses of other estrogens can relieve vasomotor symptoms, guarantee a safe endometrial pattern (when combined with progestin), and prevent bone loss *(33–47)*.

The Women's HOPE (Heart, Osteoporosis, Progestin, and Estrogen) Study, a 2-yr prospective, randomized, trial involving 2805 postmenopausal women aged 40–65 yr, looked at effects of 0.45 and 0.3 mg of CEE, both alone and combined, on vasomotor symptoms, vaginal atrophy, metabolism, endometrial response, and bone density. The standard CEE dose was compared with a three-quarter dose (0.45 mg) as well as a half dose (0.30 mg), with and without a progestin, varying from the most commonly prescribed 2.5-mg dose to a lower dose of 1.5 mg. Data from this study demonstrate that lower doses are effective, safe, and appropriate for many postmenopausal women in this age group *(33–35)*. The subjects recruited for the HOPE trial were recently postmenopausal women and those with moderate to severe vasomotor symptoms had a mean age of 52.4 yr. That makes the results look even more promising for early menopausal women. With the lower doses of CEE, for both the first 12 wk and the entire study, these women experienced significant reductions in not only the mean number but also the severity score of hot flushes. These effects were very comparable, there was no significant difference between the lower doses and 0.625 mg of CEE plus 2.5 mg of MPA in the number of hot flushes reported over the 13 cycles. And with respect to severity, in the majority of cycles, the lower combination doses also provided relief comparable to that of the 0.625/2.5 combination, which is currently the most commonly prescribed dose. The control of vasomotor symptoms was achieved for the most part within the first 3 wk in all the active treatment groups as compared with the placebo group. The effects of the lower combination regimens were very similar to those of the 0.625/2.5 dose. The number of "hot flush responders"—women who had 100% resolution of their hot flushes—was also very similar for all the combination regimens. After 3 wk of treatment, 40–50% of the women taking the 0.45- and 0.3-mg combinations had no hot flushes, and by the fourth month the percentage free of hot flushes on these regimens was up to about 60% *(34)*. However, the HOPE trial does not provide a direct measurement of QoL.

Table 3
Effects of Low-Dose HRT in Postmenopausal Women

1. Improves vasomotor and other clinical symptoms
2. Positively affects mood and quality of life
3. Improves sleep pattern
4. Restores normal bone turnover
5. Prevents postmenopausal bone loss
6. Minimizes side effects

The Low-Dose HRT and QoL

In a series of studies the effects of LD-HRT on QoL in postmenopausal women have been evaluated by the validated Italian version of the Women's Health Questionnaire *(44–46)*. In these trials the effects of low-dose conjugated estrogens and 17β-estradiol on QoL were assessed in symptomatic early postmenopausal women *(44–46)*.

Particularly, the effects of low-dose conjugated estrogens (0.3 mg/d) in a continuous combined association with different low-dose progestins (5 mg dydrogesterone; 2.5 mg of medroxyprogesterone acetate, 2.5 mg of nomegestrol; $n = 30$ in each group) were tested in healthy postmenopausal women (Table 3). The control group consisted of women receiving a daily supplement of calcium (1000 mg/d, $n = 30$). There were no significant differences in age, BMI, hormone values, smoking habits, blood pressure, education, life style, family history of breast cancer, osteoporosis, and cardiovascular diseases present in the two groups (data not shown). QoL was evaluated by the Women's Health Questionnaire handed to the women during a visit to the center. No major

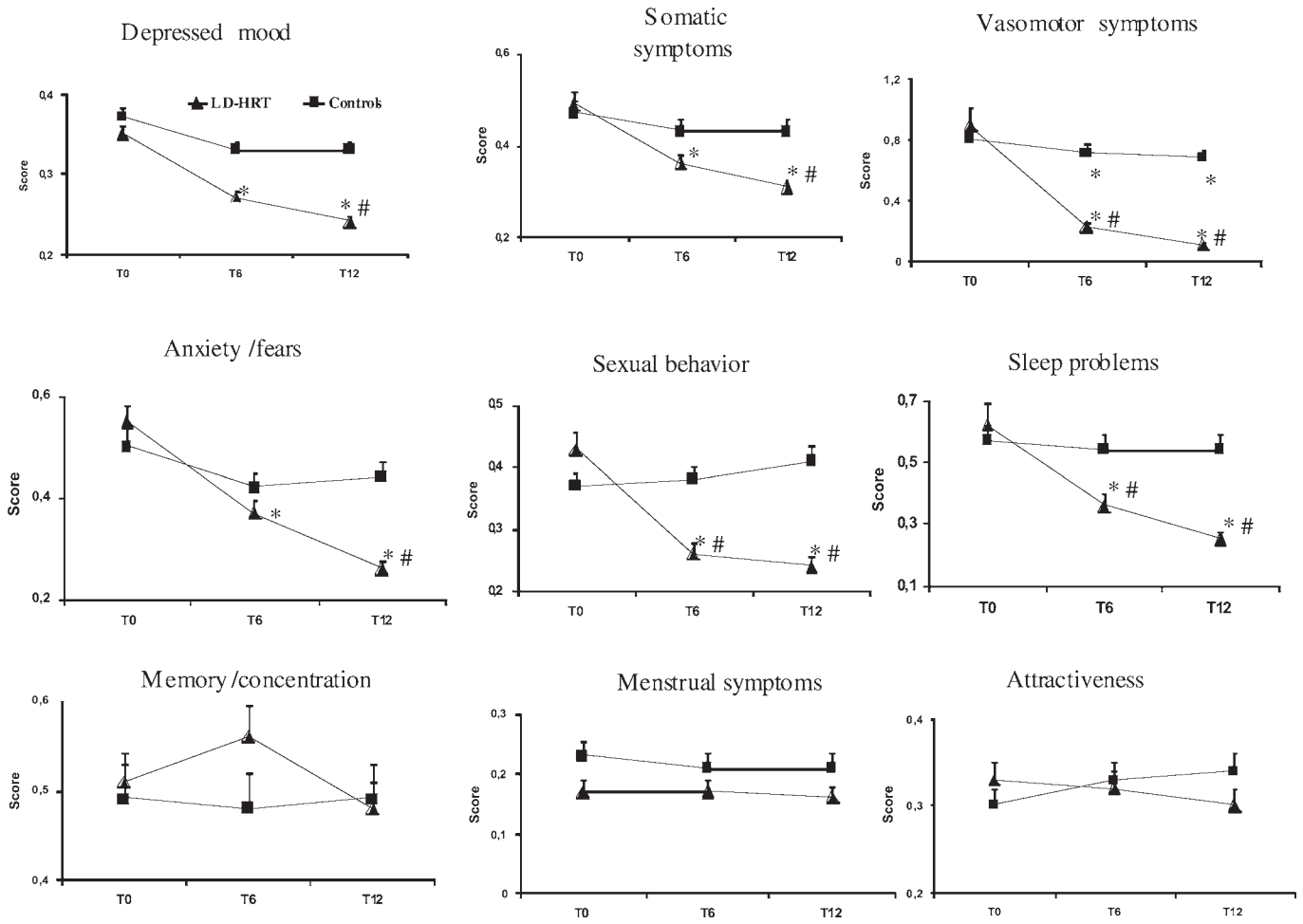

Fig. 4. The Women's Health Questionnaire results (mean ± SE) at baseline (0 wk), 6, and 12 wk in early postmenopausal women in control group ($n = 25$) and in the LD-HRT group. Control group = postmenopausal women receiving 1000 mg of calcium per day ($n = 25$); LD-HRT = postmenopausal women receiving oral 0.3 mg/d of conjugated estrogens plus a low dose of different progestins ($n = 83$). The results are reported for the valid completers. *$p < 0.05$ vs corresponding baseline levels; #$p < 0.05$ vs. corresponding control group values.

differences in the results obtained in women treated with different progestins. Therefore, the results were analyzed as a group. Women treated with 0.3 mg of conjugated estrogens showed a significantly better QoL in almost all the scores of the Women's Health Questionnaire, with the only exceptions of menstrual symptoms, memory/concentration, and attractiveness (Fig. 4) *(44–46)*. LD-HRT users showed highly significant better outcomes in those areas which are more directly attributable to hypoestrogenism, namely vasomotor symptoms and sexual problems (Fig. 4). In particular, LD-HRT users showed a lower probability of reporting anxiety/fears *(44–46)*. The overall picture emerging from this analysis suggests that LD-HRT can be of benefit for many of the postmenopausal mood changes, sexual problems, and vasomotor symptoms (Fig. 4). In addition, the null effect of LD-HRT on the menstrual symptoms' item is relevant. In fact, this item refers to all the bothersome signs and symptoms (bloating, cramping, vaginal discharge, etc.) that can be referred to "menstruation" and "hormones," often reported by postmenopausal women treated with conventional HRT doses. Thus, this is an indirect demonstration that LD-HRT can minimize the side effects correlated to hormone use, at least at the standard doses actually used.

Although a randomized trial with a head-to-head comparison was not performed, no major differences were found in these studies according to the different estrogen used (17β-estradiol or conjugated estrogen).

Low-Dose HRT and Sleep Disturbances

Insomnia, disturbed sleep, and mood alterations are significantly more frequent in perimenopausal than in premenopausal women *(47,48)*. Perimenopausal subjects experience longer and more numerous arousals resulting in significantly less sleep, with a significant correlation between sleep and mood changes *(47–52)*. The most common problems are

frequent nocturnal awakenings with difficulty returning to sleep and sometimes difficulty falling asleep *(53,54)*. Sleep disturbances with reduced sleep efficiency and increased REM sleep latency in peri- and postmenopausal women may result from hormonal changes, vasomotor symptoms, and possibly psychological factors *(56,57)*. Several studies indicate that estrogen therapy given during the perimenopausal or menopausal period can diminish not only hot flushes, but also anxiety, fatigue, depressive symptoms, enhancing mood and subjective sense of well being *(58–63)*. Improvement of psychological symptoms, cognitive functions and sleep by HRT could be the consequence of a decrease of vasomotor symptoms. Although many age-related conditions should be considered when treating postmenopausal sleep disorders *(64)*, HRT seems to diminish the disruption of sleep in climacteric women *(65)*. Conflicting results have been reported concerning the effect of different forms of HRT on sleep quality, efficiency, and various sleep architecture variables *(66–74)*. Recently, it has been reported that in postmenopausal women treated with standard dose conjugated estrogens (0.625 mg/d) in association with micronized progesterone the quality of sleep improved better than with the same estrogen dose associated with medroxyprogesterone acetate *(75)*. Specifically, with the polygraphic recordings of sleep parameters, it was demonstrated that the women treated with the estrogen plus micronized progesterone combination had fewer awakenings and showed significantly less time spent awake throughout the night *(75)*. However, recent data also clearly indicate that even a lower conjugated estrogen dose may have value in the treatment of menopausal women in which sleep disturbances are a prevalent symptom of estrogen deprivation *(46)*. In addition, the progestogen choice can make the difference in terms of effectiveness. In fact, low-dose CE (0.3 mg/d) in association with micronized progesterone (100 mg/d) in a continuous combined schedule, resulted in a more positive effect on sleep disturbances than the same conjugated estrogen dose in combination with MPA *(46)*. It must be noted that the pretreatment score values for the estrogen plus MPA group were similar to those for subjects treated with conjugated estrogen plus micronized progesterone for all items, including sleep *(46)*. Thus, the choice of progesterone/progestin is crucial for the ultimate action of HRT on sleep disturbances also using the low-dose combinations. There is a rationale to explain why micronized progesterone will be superior to MPA and other progestogens in restoring a better sleep. Progesterone is one of several steroids that target the brain, and progesterone metabolites (not found in syntheric progestogens), allopregnanolone and pregnanolone, induce anxiolytic and hypnotic effects, modulating neuronal firing through interactions with cell surface receptors for gamma-amino-butyric acid (GABA) *(76–78)*. The GABA-mimetic action of natural progesterone and its metabolites suggest that these neurosteroids act as inhibitory neurotransmitters that modulates specific neuronal functions, involved in the control of sleeping, eating, anxiety, and aggression *(76–78)*.

Accordingly, low-dose conjugated estrogen plus micronized progesterone may better improve sleep disturbances associated with menopause. Since the key point of an improved use and compliance of HRT is the personalization of schemes, doses, and type of hormones prescribed, as clinicians, we should bear in mind that all progestogens have different characteristics and biological actions, with different selectivity and potency for the different progesterone as well as mineralcorticoid, androgen, and estrogen receptors. Thus, low-dose estrogen associated with low-dose micronized progesterone may especially benefit women who complain about disturbed sleep *(46)*.

Conclusion

In future studies the assessment of QoL will be an essential tool along with clinical and laboratory evaluation, for estimating the efficacy of therapy. LD-HRT has the potential of improving not only symptoms, but also more general aspects of physical and psychological well-being, minimizing the side effects correlated to hormone use, at least at the standard doses actually used (Table 3). Further therapeutic strategies should take into account that at a time, when mid-aged women are both culturally aware of the negative aspects related to the menopause and need to maintain a good level of social and physical functioning, patient-centered evaluation is more and more important, in order to be able to provide information on how the treatments proposed affect different aspects of QoL. The demonstration of efficacy of LD-HRT provides important information for the treatment of postmenopausal syndrome. Future research should focus on the efficacy of early initiation and continuation of low-dose HRT on osteoporotic fractures and other relevant health outcomes. LD-HRT is well tolerated, with few adverse events and early bleeding control, which is likely to improve compliance with treatment. The safety of the standard higher doses used in the past, as well as in the HERS and WHI trials, cannot vaguely be referred to newer HRT schedules with lower dosages. The choice of lower estrogen doses may at least in part reduce the stimulation of breast tissue, and the activation of the haemostatic and thrombotic cascade, while maintaining the clinical effects and the bone sparing action of conventional HRT. However, data on this point are missing. Long-term prospective trials will clarify the safety of lower dose HRT.

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