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INVITED REVIEW

Impact of hormone therapy on quality of life after menopause

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Abstract

Objective: Given the complexity of the literature on quality of life (QOL) and hormone therapy (HT) among women in the menopausal transition and postmenopause, the purposes of this integrative review were to (1) define QOL as a multidimensional construct; (2) review validated instruments for measurement of QOL; (3) review results of HT and QOL clinical trials that have used validated instruments; and (4) assess the effectiveness of HT on QOL, including health-related QOL (HRQOL), menopause-specific QOL (MSQOL), and global QOL (GQOL).

Methods: The literature on HT and QOL was searched for definitions of QOL and validated instruments for measuring QOL, and the results were summarized. The purposes of this integrative review were to evaluate the effects of HT on HRQOL, differentiating the effects of HT on GQOL, HRQOL, and MSQOL. As a basis for this review, we searched for published controlled clinical trials in which the effects of HT on QOL were studied using validated QOL instruments, in particular menopause-specific validated instruments.

Results: Clear definitions are elucidated. Validated instruments for the measurements of HRQOL, GQOL, and MSQOL are summarized, and the necessity of their incorporation into future research and clinical practice is emphasized. The published effects on QOL of estrogens and progestogens administered to symptomatic and nonsymptomatic women in the menopausal transition and beyond are reviewed.

Conclusions: The impact of various health state–related symptoms on HRQOL and GQOL is now an integral component of contemporary health care. Effects of HT include GQOL and HRQOL and should be menopause-specific. There is clearly a need for further studies on menopause and menopause-related therapies using appropriate and validated instruments. Literature review shows that HT provides a significant benefit for MSQOL in midlife women, mainly through relief of symptoms, but treatment also may result in a global increase in sense of well-being (GQOL). HRQOL benefits are contingent on symptom status, as are MSQOL outcomes. Women who are severely symptomatic experience a significant improvement in HRQOL and MSQOL, although this improvement is not significant among women without severe symptoms at baseline measures in clinical trials.

Key Words: Quality of life – Menopause – Hormone therapy – Validated quality-of-life instruments.

The primary objective of contemporary health care—beyond "do no harm"—is enhancement of quality of life (QOL). Like pain, an individual's perception of "quality of life" is difficult to define. There has been no universal agreement on what QOL is and how it can be quantified. How individuals perceive their sense of QOL depends on multiple factors, which in turn affect their functioning, including satisfaction with the health care provided. Indeed, perception of QOL may be a determinant of adherence to a prescribed plan of health care. In turn, adherence to therapy should reduce the incidence of the problem it is designed to prevent or treat. Conversely, the presence of a symptomatic problem is likely to have a negative impact on the sense of QOL.[1] For example, there is considerable evidence that complications of osteoporosis will have a negative impact on the sense of health-related QOL (HRQOL). Conversely, it is less well recognized that the sense of QOL will actually affect osteoporosis.[2]

QOL has become increasingly valued as a therapeutic outcome. Effects of hormone therapy (HT) may include general QOL and HRQOL. General QOL or global QOL (GQOL) reflects one's beliefs about functioning and achievements in various aspects of life, an overall sense of life satisfaction, and well-being.[1] HRQOL is defined as a perception of life aspects that are most likely to be affected by changes in health status and is a multidimensional construct consisting of physical health and function, emotional function, role limitations, and social functioning. These dimensions of HRQOL can be mediated by symptoms, personal factors, and environmental factors.[3] Studies of menopause-specific QOL (MSQOL) use symptoms, such as hot flashes, as prompts to elicit their impact on burden or interference.

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Clearly, traditional objective measures of the efficacy of medical therapies and interventions, such as incidence of adverse effects and morbidity, death rates, and so forth, do not measure an individual's own sense of overall life satisfaction and are therefore no longer, in themselves, adequate comprehensive indicators of treatment success. The impact of a therapy on QOL now needs to be measured in research (eg, in drug trials), by health insurers (to determine the justification for reimbursing expenditures related to the treatment in question), or by clinicians (to measure the efficacy of the care that they provide).

For an accurate measurement of the impact of a condition or therapy on QOL, it is mandatory that QOL be precisely defined and that validated instruments be used to measure QOL changes in a consistent, reproducible, and directly related manner. Such instruments are reviewed and listed in Appendix 1.

Optimal care of women through the menopausal transition requires assessment of changes in QOL by monitoring and measuring changes across the domains of physical, behavioral, cognitive, and emotional functioning. The importance of broadband assessments of the effective practice of menopausal medicine has been widely recognized in the growing literature on QOL. The literature is far from perfect, with many studies open to criticism. Nonetheless, there is now a large body of data, and our intention has been to review all that information to present the current state of knowledge. Never has clinical evaluation of QOL been more pivotal than at this time when the use of hormone treatment strategies has come under fire and women and physicians alike are searching for evidence of positive outcomes.

OBJECTIVE

The primary objective of this integrative review of the healthcare literature in the past decade is to critically evaluate and summarize current knowledge of the impact of estrogen and estrogen-progestogen (E + P) therapies on women's QOL after menopause. In particular, we focused on those studies that used validated instruments to determine the impact of HT on the components of QOL.

To adequately appreciate the QOL literature, we need to understand the validated instruments pertinent to this population, hence the greater details provided in Appendix 1.

Given the complexity of the literature on QOL and HT, the purposes of this review are as follows:

1. Define QOL as a multidimensional construct
2. Review validated instruments for measurement of QOL
3. Review results of HT and QOL clinical trials that have used validated instruments
4. Assess the effectiveness of HT in QOL, including HRQOL, MSQOL, and GQOL

DEFINITIONS OF QOL

QOL has many definitions, depending on the theoretical perspective taken. Menopause is not a disease, being essentially a transition in life, and QOL is related to more than health. The World Health Organization 1993 definition of an individual's perception of one's life status in the context of the culture and value systems in which one lives and in relation to one's goals, standards, and concerns can be applied to postmenopausal women.[4]

The QOL experienced by women during the menopausal transition and postmenopause is usually described as HRQOL and includes physical health and functioning, emotional functioning, and role limitations. In this context, the term "quality of life" inappropriately refers to menopausal symptoms, such as the presence of significant hot flashes, night sweats, vaginal dryness or pain, and loss of well-being. These menopause-related symptoms may negatively affect QOL in symptomatic postmenopausal women and often improve with HT. However, it is important to recognize these symptoms along with other more global aspects of QOL beyond health status, including life satisfaction, coping, and psychological functioning—referred to as GQOL. The point is that symptoms themselves do not denote QOL but instead may modify QOL.

The term "quality of life" should be defined by measurable domains. Moreover, these domains should be evaluable independent of the presence or absence of disease or symptoms—although these, of course, might influence QOL. Thus, QOL refers to a global sense of well-being and self-satisfaction beyond the presence or absence of symptoms. It also determines how a perimenopausal or postmenopausal woman feels generally and specifically regarding interest in life, ability to complete a days' work with satisfaction, maintenance of good interpersonal relationships, sexuality, and a general feeling of wellness.

A health/illness model looks at the effects of ill health on a number of symptom parameters such as those measured in symptom-profile instruments.[5-7] HRQOL represents those parts of QOL that directly relate to an individual's health (ie, the effects of their physical and emotional states on their overall QOL). Because somatic symptoms may negatively impact the perception of QOL, it is essential that somatic symptoms be accurately identified and measured during the clinical assessment of QOL. Indeed, most clinicians treating women experiencing the menopausal transition or postmenopause use some form of menopause symptom checklist.

In an effort to identify the impact on QOL of therapies for menopause-related symptoms, investigators have developed measures of MSQOL. MSQOL refers to the QOL estimated by women experiencing the menopausal transition or early postmenopause, using measures to assess bother and interference with multiple dimensions of daily life that are linked to symptoms reported by women during the menopausal transition and are exemplified by the Menopause-Specific Quality of Life (MENQOL) Questionnaire[8,9] and the Women's Health Questionnaire (WHQ).[6]

GQOL refers to an individual's perception of her position in life in the context of the culture and value systems in which she lives and in relation to her goals, standards, and concerns.[4] GQOL denotes individual perceptions, as experienced by the person, and is not an objective measure. Recent efforts to assess GQOL in ways that are appropriate for midlife women

culminated in the development of the Utian Quality of Life Scale (UQOL).[10]

VALIDATED INSTRUMENTS FOR MEASURING MSQOL

Specific instruments have been validated to measure different aspects of QOL (Appendix 1). Instruments that have been developed and validated to measure both HRQOL and GQOL can be either generic, applicable to broad population groups, or disease-related or specific population–related. Instruments validated specifically for perimenopausal and postmenopausal populations are usually termed MSQOL tests.[11]

Simply using a checklist of symptoms can introduce bias because many will respond positively to symptoms on a checklist, but the reporting rate will decrease if frequency or bothersomeness of symptoms is included. A standardized list of symptoms is required to elicit comparable data from each participant and to compare results across studies.

For adequate measurement of QOL, an instrument needs to be modern, applicable, and reliable, with normal values for different populations. It also must show change over time or with different interventions. The instrument should be comparable with other validated instruments and responsive to changes in clinical symptoms over time. Failure to use adequately validated rating scales has been a major problem in menopause research.

Standardized menopause-specific instruments that measure symptoms of the menopausal transition and postmenopause need to satisfy factor analysis criteria, to include subscales measuring different aspects of symptoms and sound psychometric properties, and to be standardized across populations of women.[11]

Domains should be evaluable independent of the presence or absence of disease, handicap, or symptoms, even though these might influence QOL.[1,10] In this respect, GQOL refers to an overall sense of well-being and self-satisfaction beyond the presence or absence of symptoms. It also determines how perimenopausal or postmenopausal women feel generally and specifically regarding interest in life, ability to complete a days' work with satisfaction, maintenance of good interpersonal relationships, sexuality, and a general feeling of wellness.

HRQOL is an important outcome in the evaluation of both function and disease progression among healthy and ill populations. Measures of HRQOL typically denote aspects of life that are most likely to be affected by changes in health status. Measurement of HRQOL is multidimensional, consisting of the following domains: physical health and functioning, emotional functioning, role limitations, and social functioning.[12]

Another mechanism for evaluating QOL-related healthcare outcome is to determine the level of cost-effectiveness of a specific therapy or intervention. Quality-adjusted life years, a measure of disease burden that includes both the quality and the quantity of life lived, can be used to assess treatment effects, and the ratio of cost to efficacy can thus be determined. Moreover, a cost-effectiveness ratio can be developed for each of several potential therapies, and these ratios can be ranked to compare the value of each therapy.[13,14]

The earliest large randomized clinical trials of HT included several varieties of QOL measures. Among these are measures of HRQOL, such as the MS36, an instrument reflecting health-related effects on functional capacity. Other trials have incorporated measures of MSQOL, such as the MENQOL Questionnaire[8] and the WHQ.[6] To date, a limited number, such as the UQOL, have incorporated measures reflecting general QOL or GQOL.[10]

In summary, HRQOL is a person's perception of one's physical, cognitive, and mental health. GQOL is a broader measure of a person's overall sense of life satisfaction that incorporates a general sense of well-being in the presence or in the absence of symptoms or impairment. Menopause-specific measures of QOL (MSQOL) are age-appropriate instruments validated for midlife women that reflect the impact of symptoms experienced during the menopausal transition and early postmenopause (ie, HRQOL instruments validated for midlife women).

Only those instruments that have been validated for specific populations or circumstances can be appropriately used. Thus, the MENQOL Questionnaire, the Greene Climacteric Scale, or the UQOL applies to perimenopausal and postmenopausal populations. An ideal profile can best be generated by a combination of a validated HRQOL menopause symptom profile (eg, Greene Climacteric Scale) and a GQOL instrument (eg, UQOL). This allows clarification of the relationship between each instrument and change or progress over time. Unfortunately, published studies directly using such an approach are as yet lacking in the health science literature.

It is important to emphasize that summing individual items from different domains of any specific instrument will produce meaningless results. Greene, a pioneer in the validation of HRQOL instruments, presented an example: In trying to measure overall "size" by extracting and adding a person's height and weight measurements from a domain, the resultant measure would fail to distinguish tall, thin people from small, obese people because they both would tend to have a similar overall "size" score. Selective extraction of items, in essence, produces a new but nonvalidated instrument.[15] For example, extracting symptoms of headache and anxiety from separate domains of one instrument and using the combination as a measure of psychological stress during menopause would be quite inappropriate. Indeed, extracting even one question, such as one relating to sexual function, and then using that as a measure of the sexual impact of a drug would be equally unacceptable.

INTEGRATIVE REVIEW

Methods

A purpose of this integrative review was to evaluate the effects of HT on HRQOL, differentiating the effects of HT on general QOL or GQOL, HRQOL, and MSQOL. As a basis for this review, we searched for published controlled clinical trials in which the effects of HT on QOL were studied. We searched PubMed/Medline using headings related to both HT (including estrogen and E + P) and QOL, specifying the following inclusion criteria: full-text publication in English available, year of

TABLE 1. *Summary of clinical trial data about HT and QOL: study, sample, trial design, outcome measures, and results*

Study	Sample: recruited, randomized, completed	Trial design: treatment and control conditions	Outcome measures	Results
Clinical trials: HRQOL				
Hlatky et al[16]	HERS: 2,763 postmenopausal women with CHD; mean (SD) age, 67 (6.6) y	Randomized to CEE + MPA (n = 1,383) vs placebo (n = 1,383) for 36 mo	Physical activity, energy/fatigue, mental health (Rand 36 scales), depressive symptoms	More rapid decline to year 3 in physical function and energy/fatigue scores in women assigned to HT; no treatment effect on mental health; HT effects on QOL measures depended on symptom status at baseline; women with hot flashes at baseline had improved mental health and lower depression scores; women without hot flashes had reduction in physical functioning and emotional functioning; all women's scores in physical functioning, mental health, and energy/fatigue declined for 3 y, but there was no change in depressive symptoms
Hays et al[17]	WHI: 16,608 postmenopausal women aged 50-79 y randomized to CEE + MPA vs placebo; subset (n = 1,511) provided outcomes on year 3	Randomized to CEE + MPA vs placebo pills; masked	Rand 36 (MS36) scales	At 3 y, no significant differences in Rand 36 scales; small but no clinically meaningful benefits in physical function, bodily pain, and sleep at 1 y; hot flashes improved
Brunner et al[18]	WHI: 10,739 postmenopausal women aged 50-79 y posthysterectomy; CEE (n = 5,300) vs placebo (n = 5,429); 78% and 82% of the adherent subset (n = 1,189) provided outcomes on year 3	Randomized to CEE vs placebo pills; masked	Rand 36 (MS36) scales	No significant difference in MS36 scales at 3 y; CEE effects greater than placebo effects for sleep ($P < 0.001$), but there was no clinically significant difference
Archer et al[19]	1,147 women with intact uterus and not on HT; mean (range) age, 56 (42-75) y; evaluated and randomized to 1.0 mg of E_2 alone (n = 226) or 1.0 mg of E_2 plus 0.5 (n = 227), 1.0 (n = 231), 2.0 (n = 227), or 3.0 (231) mg of drospirenone; 149, 179, 169, 173, and 175 completed the study medication; 1,147 women with intact uterus; 845 completed the medication; mean (range) age, 56 (42-75) y	E_2 and E_2 combined with varying doses of drospirenone	SF-36 and WHQ administered on visits 1, 4, 5, and 13	Mean changes in SF-36 scores not significant across groups at each time point; compared groups treated with drospirenone with those treated only with E_2; mean changes in physical and mental health not significant; all groups improved on vasomotor symptoms and sleep problems across all time points; no significant WHQ global score; overall positive mean change in psychological and somatic symptoms, but global changes not significant; details of between-group differences not given; improvement in E_2-only–treated vs drospirenone-treated women at cycle 13
Ylikangas et al[20]	419 postmenopausal women; mean age, 56 y; of 257 women who participated in the original trial, 208 enrolled at 6 y; women completed the 15D scale at 6 y; compared with 771 age-matched controls from the 2000 Finnish Health Survey	As above but switched from 2 to 1 mg of E_2 dose and from 5 to 2.5 mg of MPA after 8.5 y; study treatment stopped after 9 y	15D scale	Continuous-combined HT associated with significantly better HRQOL after 6 and 9 y of treatment; mobility, breathing, sleeping, eating, speech, usual activities, mental function, discomfort, symptoms, depression, distress, vitality, and sexual activity in the HT-treated group were better than those in age-specific matched controls; women who discontinued continuous-combined HT at 9 y experienced poorer levels of mobility, vision, hearing, sleeping, depression, and vitality, and overall score; minimization of E_2 and MPA doses at 8.5 y were not associated with decline in HRQOL after 6 mo
Welton et al[21]	3,721 postmenopausal women aged 50-69 y with intact uterus; randomized to E + P (n = 1,862) vs placebo (n = 1,859); mean (SD) age, 64 (4) y; E + P (n = 1,043) vs placebo (n = 1,087) studied at 1 y	E + P (0.625 and 2.5 or 5 mg) vs placebo	HRQOL at 1 y from E + P (n = 1,043) vs placebo (n = 1,087); WHQ and EuroQOL EQ-5D	No significant differences in overall QOL at 1 y; slightly reduced QOL in the E + P group at 4 mo; EuroQOL EQ-5D measures with no significant differences at 1 y; slightly reduced QOL in the E + P group at 4 mo; significant improvements in WHQ for HT users: vasomotor symptoms, sexual functioning, and sleep problems

TABLE 1. *(Continued)*

Study	Sample: recruited, randomized, completed	Trial design: treatment and control conditions	Outcome measures	Results
Moriyama et al[22]	44 postmenopausal women posthysterectomy; mean (range) age, 54 (42-58) y	Randomized to physical exercise and HT (n = 9), sedentary lifestyle and HT (n = 14), physical exercise and placebo (n = 11), and sedentary lifestyle and placebo (n = 10); followed for 6 mo	HRQOL measured by the Brazilian version of SF-36 and Kupperman Index	SF-36 (Brazilian) increase in QOL/physical functioning and reduced pain in the physical exercise group; HT had no effect on HRQOL for 6 mo; HT had no effect on HRQOL, but hot flashes improved significantly in all groups for 6 mo
Menopause-specific QOL outcomes				
Welton et al[21]	3,721 postmenopausal women aged 50-69 y with intact uterus; E + P (n = 1,862) vs placebo (n = 1,859)	Randomized to E + P (0.625 and 2.5 or 5 mg) vs placebo; WHQ at 1 y (n = 1,043)	WHQ	Significant improvements in WHQ scores for vasomotor symptoms, sexual functioning, and sleep in HT users vs placebo
Battacharya and Jha[23]	119 symptomatic Indian women screened; 76 randomized to tibolone (n = 38) or E_2 gel (n = 38); women on tibolone (n = 38) and E_2 gel (n = 31) completed 44.5 (5.6) y	Tibolone 2.5 mg/d orally for 6 mo; E_2 gel (0.06%) with 2.5 g of gel containing 1.5 mg of E_2 transdermally for 6 mo	MRS II scale and subscales	Tibolone group experienced a decrease in total MRS score greater than the E_2 gel group; tibolone group improved on the somatovegetative and psychological scales
Archer et al[19]	1,147 women with intact uterus; 845 completed medication; mean (range) age, 56 (42-75) y	Randomized to 1.0 mg of E_2 alone or 1.0 mg of E_2 plus 0.5, 1.0, 2.0, or 3.0 mg of drospirenone	WHQ scale	WHQ scores: somatic scores improved more in drospirenone/E_2 vs E_2-alone groups; significant improvement in vasomotor and sleep scores within all groups; significant improvement in coping with 0.5 mg of drospirenone/E_2 vs E_2 only
Utian et al[24]	318 women with intact uterus; mean age, 53 y	Randomized to BAZ 20 mg/CEE 0.45 mg, BAZ 20 mg/CEE 0.625 mg, or placebo for 12 wk; double-blind trial	MENQOL Questionnaire	Total MENQOL scores improved in BAZ/CEE groups vs placebo
Global QOL outcomes				
Welton et al[21]	3,721 postmenopausal women aged 50-69 y with intact uterus; E + P (n = 1,862) vs placebo (n = 1,859)	Randomized to E + P (0.625 and 2.5 or 5 mg) vs placebo; WHQ at 1 y (n = 1,043)	EuroQOL EQ-5D VAS (0 = *might as well be dead* to 100 = *perfect QOL*)	Women receiving placebo were significantly better at 4 and 14 wk; no significant differences at 52 wk

HT, hormone therapy; QOL, quality of life; HRQOL, health-related QOL; HERS, Heart and Estrogen/progestin Replacement Study; CHD, coronary heart disease; CEE, conjugated equine estrogens; MPA, medroxyprogesterone acetate; WHI, Women's Health Initiative; E_2, estradiol; SF-36, MOS 36-item Short-Form Health Survey; E + P, estrogen-progestogen; WHQ, Women's Health Questionnaire; MRS, Menopause Rating Scale; BAZ, bazedoxifene; MENQOL, Menopause-Specific Quality of Life; VAS, visual analogue scale.

publication dating from 2002 to 2012, and controlled clinical trial design or comparative effectiveness study design that includes HT as one of the treatments being evaluated. References cited in published trials were studied for links to additional trials not identified in the literature search. Full-text publications were obtained for data extraction. Data extraction included the elements presented in Table 1:

- Study, including the name of the authors and the year/location of trial
- Sample characteristics and size, including the numbers screened, randomized, completing treatment, and completing follow-up data collection
- Trial design, including intervention and duration of treatment and control or comparison conditions
- Outcome measures used to assess QOL
- Results, including major findings regarding the efficacy of the intervention for QOL, including significant differences between treatment and control groups or multiple treatment groups

Analysis

Data were analyzed by reviewing the patterns of effects on QOL, as measured by indicators of HRQOL, symptom-specific QOL, and general QOL. Given the relatively small number of identified clinical trials that used the same HT preparations and the same measures of QOL, meta-analysis was not appropriate.

Results

Published results from nine separate clinical trials that included HRQOL outcomes were identified.[16-22] By far, the largest of these studies was the Women's Health Initiative (WHI)[17,18] followed by the Heart and Estrogen/progestin Replacement Study (HERS),[16] both of which were conducted in the United States. In addition, there was a large trial in Europe comparing the effects of E + P with the effects of placebo.[21] One trial compared different doses of estradiol and medroxyprogesterone

acetate (MPA),[20] one trial compared HT with placebo with or without exercise in sedentary women,[22] and another trial compared estradiol alone with estradiol and drospirenone and estradiol[19]—all focusing on HRQOL. Four trials examined MSQOL outcomes,[21-24] and only one published trial estimated the effects of HT on GQOL[21] (Table 1).

HRQOL and HT

In most trials examining HT effects on HRQOL, outcomes were assessed using the MS36 (Rand 36) scales,[7] including physical functioning, emotional functioning, physical activity, and energy/fatigue, among others. Because most women in trials examining HRQOL were 60 years or older and participants in a primary or secondary prevention trial for chronic disease,[16-18] these measures of HRQOL were appropriate. For women in the WHI trials, at 3 years after randomization, the MOS 36-item Short-Form Health Survey (SF-36) scores were not significantly different for women using either estrogen alone or E + P compared with those randomized to placebo in the WHI trials.[17,18] The main effects of HT on HRQOL were not significant in these trials, with few exceptions. In HERS, women treated with conjugated equine estrogens (CEE) and MPA experienced a more rapid decline in physical function and energy/fatigue than those assigned to placebo. In contrast, a subset of women troubled by symptoms such as hot flashes at baseline experienced improvement in mental health, in contrast to women without hot flashes who experienced reduced physical and emotional functioning.[16] In a trial of different doses of estradiol and MPA, there were no significant differences in HRQOL associated with minimizing the estradiol and MPA doses after 8.5 years of prior treatment.[20] Among the trials measuring HRQOL, the WHI was the largest, followed by the studies by Welton et al[21] (n = 3,721), HERS (n = 2,763), and the trial by Archer et al[19] (n = 1,147). Thus, the sample sizes for several of these trials were adequate to determine clinically significant effects. Also, the larger studies included assessments of CEE with MPA or CEE alone or estradiol.

Menopause-specific QOL

Studies of the MSQOL effects of HT[19,21-24] have been informative about dimensions of bother and interference with multiple dimensions of life that one attributes directly to one or more symptoms. In a small number of trials, HT was associated with a significant improvement in MSQOL, as measured by the WHQ, the MENQOL Questionnaire, and the Menopause Rating Scale (MRS). Participants in these trials tended to be somewhat younger than most participants in trials assessing HRQOL outcomes and tended to have been recruited because they were experiencing hot flashes. These trials assessed the effects of CEE and estradiol, and two of four studies had sample sizes exceeding 1,000.

Global QOL

We found only one published clinical trial of estrogen therapy effects on GQOL.[21] In this trial, a single item was used to estimate GQOL. There was no significant difference in GQOL after 52 weeks of treatment, and women randomized to the placebo group reported better QOL at 4 and 14 weeks compared with those randomized to E + P. At this time, it is not possible to reach a definitive conclusion as to whether HT improves GQOL beyond its impact on menopause-specific HRQOL.

DISCUSSION

HRQOL has become an important outcome in clinical trials and a significant consideration in prescribing therapy for menopause-related symptoms. Studies published to date have included a broad diversity of instruments for measuring QOL, and drug types and formulations have also differed. Given the relatively small number of identified clinical trials that used the same HT preparations and the same measures of QOL, meta-analysis was not appropriate. An integrative review of published controlled clinical trials of HT indicates that, although HRQOL does not improve significantly in response to HT, MSQOL indicators do. Indeed, published trials indicate that HT can provide a significant benefit on MSQOL for midlife women, mainly through relief of symptoms. To date, the effects of HT on GQOL are not supported by data adequate to determine therapeutic effects.

The earliest large randomized clinical trials of HT included several varieties of QOL measures. Among these were measures of HRQOL such as the MS36,[12] an instrument reflecting health-related effects on functional capacity. Other trials have incorporated measures of MSQOL, such as the MENQOL Questionnaire[8,9] and the WHQ.[6] The UQOL is a menopause-specific measure of GQOL.[10] To date, only one published trial has incorporated measures reflecting general QOL or GQOL into postmenopausal HT.[21]

This integrative review of published controlled clinical trials of HT indicates that, although HRQOL does not improve significantly in all women enrolled in trials of HT for primary or secondary prevention of chronic disease, a subset of women who had hot flashes at baseline does experience improvement in symptoms. Those women without hot flashes at baseline experience a greater decline in physical functioning and emotional functioning when treated with HT than do women with hot flashes.[16]

Studies of HT effects on MSQOL indicators demonstrate significant benefits for midlife women, mainly through relief of symptoms.[19,21,23,24] For example, Welton et al[21] demonstrated significant improvements in WHQ scores for vasomotor symptoms, sexual functioning, and sleep problems among HT users, but no improvement in overall QOL after 1 year of HT. Similarly, Battacharya and Jha[23] found that women randomized to estradiol gel for 6 months experienced less reduction in total MRS scores than women treated with tibolone. Archer et al[19] found that women treated with estradiol and estradiol combined with varying doses of drospirenone all experienced improvement in WHQ scores for vasomotor, sleep, psychological, and somatic symptoms. Utian et al[24] found improved scores on the MENQOL Questionnaire for women treated with bazedoxifene and CEE versus placebo. Taken together, these studies support improvement in MSQOL attributable to symptom management.

These results suggest that the primary mechanisms by which HT influences QOL for midlife women and older women differ. In studies of women whose mean age is older than 60 years and thus are more likely to have HRQOL assessed by measures of their functional capacity, HT effects on HRQOL seem to be moderated by symptom status. Those who were troubled by hot flashes at the beginning of treatment experienced less decline in physical functioning and emotional functioning, as measured by the Rand 36 scales, than those who did not report hot flashes.[16] Thus, it is possible that symptom relief influences HRQOL even in women who have experienced menopause in earlier decades of life.[25]

To date, the effects of HT on GQOL are not supported by data adequate to determine therapeutic effects. Unpublished preliminary reports from the Kronos Early Estrogen Prevention Study indicate a trend toward improvement in GQOL (as measured by the UQOL) with CEE, but these differences are not statistically significant.[26] Future clinical trials incorporating GQOL measures as outcomes will help assess the use of HT for enhancing GQOL.

CONCLUSIONS

The impact of various health state–related symptoms on HRQOL, MSQOL, and GQOL is now an integral component of contemporary health care. Effects of HT include GQOL and MSQOL, both being equally relevant to determining an overall sense of well-being. There is clearly a need for further studies on menopause and menopause-related therapies using appropriate and validated instruments. In the absence of a new single menopause-specific validated instrument that measures both HRQOL and GQOL, future studies should use separate instruments to measure both.

A review of the present literature shows that HT provides a significant benefit on MSQOL in midlife women, mainly through relief of symptoms, but treatment effects on a global increase in women's sense of well-being (GQOL) need to be evaluated in additional studies. HRQOL benefits are contingent on symptom status, as are MSQOL outcomes. Women who are severely symptomatic experience a significant improvement in HRQOL and MSQOL, although this improvement is not significant among women without severe symptoms at baseline measures in clinical trials.

APPENDIX 1

Generic scales

Nowadays, researchers tend to use menopause-specific instruments in menopause-related research. Nonetheless, a few generic instruments are still being widely used. Two examples (HRQOL scales) are briefly described below:

- The SF-36 is a pure symptom inventory and is used to evaluate QOL in older populations with chronic disease. Frequently used as a symptom profile survey, it has been validated with eight domains, four of each summarizing overall measures of physical health (physical functioning, role physical, bodily pain, general health) and mental health (vitality, social functioning, role emotional, mental health). A common error in research has been the extraction of items from the SF-36, in essence creating a new nonvalidated instrument (based on the example of adding height and weight above).[7]
- The EuroQOL EQ-5D is a multidimensional instrument that measures five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), each at three levels (*no problem* to *extreme problem*). In addition, it includes a visual analogue scale ranging from the *worst imaginable state* to the *best imaginable state*.[27]

MSQOL scales

- The Greene Climacteric Scale uses factor analysis as basis to categorize symptoms into three factors (vasomotor, somatic, and psychological) and currently consists of 21 symptoms, each rated on a four-point scale of severity. Test-retest reliability coefficients of subscales achieve a satisfactory level. Its validity has been proven over time. This scale is an excellent replacement for the Kupperman Index.[5]
- The WHQ is based on a factor analysis of 36 symptoms reported by a general population sample from southeast England. There are eight subscales; four are identical to the Greene Climacteric Scale with 32 symptoms, each rated on a binary scale of 0/1. Satisfactory test-retest reliability is good. It is used as a comparative measure, demonstrating its construct validity.[6,28]
- The Menopausal Symptom List is based on a factor analysis of 56 symptoms from a general population sample of Australian women. There are three subscales (vasosomatic, general somatic, and psychological). The psychological subscale includes the anxiety and depression subscales of the Greene Climacteric Scale and the WHQ. The final version has 25 symptoms, each rated on a six-point scale of frequency and severity. Test-retest reliability is satisfactory, but validation is limited.[29]
- The MRS is based on a factor analysis of three dimensions of severity (somatic, psychological, and urogenital symptoms) from a sample of German women. The final scale consists of 11 symptoms, each rated on a five-point severity scale. The women were retested for 1.5 years with a high degree of stability in all three subscales.[30]
- The MENQOL Questionnaire is an early hybrid, largely measuring HRQOL but incorporating some domains of GQOL. It has been validated in a perimenopausal population.[8] A modified MENQOL-Intervention Questionnaire has been subsequently developed and recommended by the authors for use where intervention adverse effects might negatively impact a woman's QOL.[9]

GQOL menopause-specific scale

- The UQOL is based on a two-stage factorial process. Principal components analysis is followed by factor analysis

using 40 questions from a sample of Americans living in the East and Midwest of the United States. The final scale consists of 23 items, each rated on a five-point Likert scale. It should be used in combination with a standardized measure of climacteric symptoms.[10] The UQOL is validated in multiple languages.[31,32]

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