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Compounded bioidentical HRT improves quality of life and reduces menopausal symptoms

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Abstract

Bioidentical hormone replacement therapy, a form of hormone balancing and treatment that uses hormones identical to the ones naturally produced by the body, is an effective and well-tolerated method of hormone replacement therapy. The Marion Gluck Clinic conducted a small-scale study to assess the effectiveness of compounded bioidentical hormone replacement therapy treatment protocols and their impact on the quality of life of women experiencing symptoms of the menopause. Quality of life was assessed by completing the Greene Climacteric Scale questionnaire before and after bioidentical hormone replacement therapy treatment. Statistical significance of the data was tested using a Student's two-tailed, paired t-test. The results demonstrated a significant improvement of 52% in quality of life after bioidentical hormone replacement therapy treatment. All 21 menopausal symptoms assessed were greatly reduced after BHRT treatment. Evidence is provided showing that bioidentical hor replacement therapy, performed according to the Marion Gluck Clinic local c guidelines, improves quality of life and reduces menopause-associated symptoms in women. In addition, this pilot study paves the way for a future full-scale study, where the authors aim to assess quality of life and safety in a significantly larger number of women.

Hormone balancing using bioidentical hormone replacement therapy (BHRT) is a form of treatment that uses hormones with an identical molecular structure to the hormones naturally produced by the body, such as progesterone, estradiol and estriol, as opposed to non-bioidentical hormones that are structurally different from human hormones,

such as conjugated equine estrogen (CEE) and synthetic progestins such as medroxyprogesterone (MPA).

Data from clinical outcomes and physiological studies demonstrate that bioidentical hormones are effective and produce fewer side effects than their non-bioidentical counterparts, including a lower risk of breast cancer and cardiovascular disease (Fournier et al, 2005; **Fournier et al, 2007**; **Holtorf, 2009**).

As an example, progesterone, when compared with synthetic progestins, is associated with better clinical outcomes. Studies where women on hormone replacement therapy (HRT) were switched from synthetic progestins to progesterone reported greater satisfaction, better quality of life (QoL), and fewer side effects (**Greendale et al, 1998**; **Fitzpatrick et al, 2000**; **Cummings and Brizendine, 2002**; Lindenfeld and Langer, 2002). It is important to note that natural progesterone is reported to be as effective as synthetic progestins in protecting the endometrium from hyperplastic changes associated with estrogen-only therapy (**Judd and Meoane-Sims, 1996**).

Estriol has also been shown to have a protective effect with regard to risk of breast cancer. The protective effect of estriol relies on its high affinity to bind estrogen receptor (ER)-beta (which inhibits breast cell growth), while other estrogens, including CEE, have a preference for ER-alpha (which promotes breast cell growth) (**Paech et al, 1997**; **Paruthiyil et al, 2004**; **Bao et al, 2006**).

In addition, synthetic progestins used in non-BHRT are known to down-regulate ER-beta, which may explain why a combination of synthetic progestins with estrogens increases the risk for breast cancer (**Bakken et al, 2004**).

In regard to cardiovascular disease, the Women's Health Initiative (WHI) demonstrated that a combined hormone therapy using the non-bioidentical form of estrogen CEE with a synthetic progestin, MPA, resulted in an increased risk of heart attack and s (**Rossouw et al, 2002**; **Chlebowski et al, 2003**; **Anderson and Limacher, 2004**). been proposed that the results were skewed because of a relatively elderly population of women being given high dosages of HRT. However, it has also become apparent that the adverse outcomes observed in the WHI may be related to the type of hormones administered, ie non-bioidentical hormones (**Panay and Fenton, 2010**; **Panay, 2014**). While synthetic progestins counteract the positive effects of estrogen in cardiovascular protection, the same is not true for progesterone. In fact, bioidentical transdermal estrogen combined with progesterone is associated with beneficial cardiovascular effects (**Mueck, 2012**; **Simon, 2012**).

Therefore, although randomised controlled clinical trials of larger size and longer duration are needed to further assess its efficacy and safety, the current evidence shows

that BHRT represents an effective and well tolerated method of HRT and should be considered, particularly by women at risk of adverse side effects. In particular, compounded BHRT has gained increasing interest and popularity in recent years for managing menopausal symptoms. Compounded BHRT is a form of personalised therapy whereby the dosage, regimen, and route of administration are custom-made according to patients' hormone levels, symptoms, and preferences (**Thompson et al, 2017**).

The present small-scale study was conducted retrospectively at the Marion Gluck Clinic (MGC), a private BHRT women's health clinic based in London, to locally assess QoL in women experiencing menopausal symptoms, before and after BHRT treatment. QoL questionnaires represent an important outcome measure to quantify the effect a treatment has on symptoms and the QoL of patients.

Methods

Population

Women (n=69) aged 37–64 years old presenting with menopausal symptoms were asked to complete the self-administered Greene Climacteric Scale questionnaire using an electronic device at the MGC, before starting BHRT treatment (baseline) and after BHRT treatment (follow-up). The period between baseline and follow-up varied between 6–24 months amongst women.

Treatment received

All patients received personalised BHRT treatment via a compounding pharmacy. BHRT treatments included: estradiol/estriol/biest with progesterone, +/- testosterone and +/- dehydroepiandosterone (DHEA), according to MGC local clinical protocols. BHRT compounds varied by dose and dosage form, according to patients' hormone [redacted] detected by blood tests and accompanying symptoms. BHRT compounded prescri[redacted] were reviewed 6 weeks after starting treatment and every 3–6 months thereafter. BHRT compounds were only prescribed when no contraindications to the treatment were found.

The Greene Climacteric Scale (**Greene, 1976**) is a standardised measurement scale for menopausal symptoms. It consists of 21 questions covering three main areas: psychological, physical and vasomotor, and is commonly used to assess changes in different symptoms before and after menopause treatment. Each question is answered on a 4-point Likert scale (0-Not at all; 1-A little; 2-Quite a bit; 3-Extremely). To calculate the Greene Climacteric Scale score, answer scores to all 21 individual questions are summed to give a total score for each patient at baseline and follow-up; a

higher score indicates a worse QoL. A box-and-whisker plot was used to represent the data. Box-and-whisker plots provide a graphical summary based on the quartiles and median of the data set. Quartiles are used to split the data into four groups, each containing 25% of the measurements.

Changes in symptoms' intensity for the top two categories of the Likert scale (2-Quite a bit and 3-Extremely) were expressed in a bar chart, by comparing the percentage of patients in those categories at baseline and follow-up for each symptom.

Statistical analyses were carried out using a Student's two-tailed, paired t-test. P-values less than 0.05 were considered statistically significant.

Results

The mean age of women (n=69) aged 37 to 64 was 52 (±5.4 SD) years. Follow-up time was from 6–24 months with a median follow-up time of 11 months (±6.0 SD).

The Greene Climacteric Scale total score results are represented as a box-and-whisker plot. The lower the score in the Green Climacteric Scale, the better the QoL of a patient. The results show that there is a drop in the scores' median from 25 at baseline to 12 at follow-up, which translates as a 52% score reduction, and therefore a 52% overall improvement in QoL in women after BHRT. Statistical analysis using a two-tailed, paired t-test shows that the results are highly significant (P<0.001) (*Figure 1*).

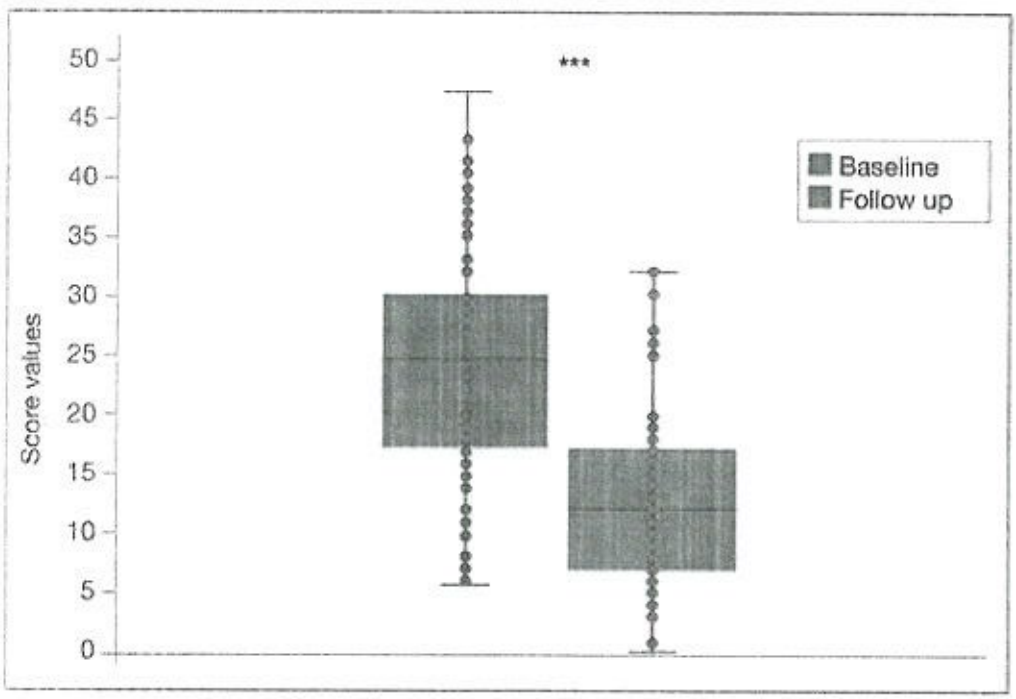

Figure 1. Green Climacteric Scale scores. Box-and-whisker plot (median, first and third percentiles, range), with the scatter plot of the raw data, of the Greene Climacteric Scale scores.

Baseline = before BHRT treatment; Follow-up = after BHRT treatment *** indicates P<0.001

Figure 2 shows changes in symptoms' intensity for the top two combined categories (2-Quite a bit and 3-Extremely) of the Likert scale by comparing the percentage of patients in those categories at baseline and follow-up, for each symptom.

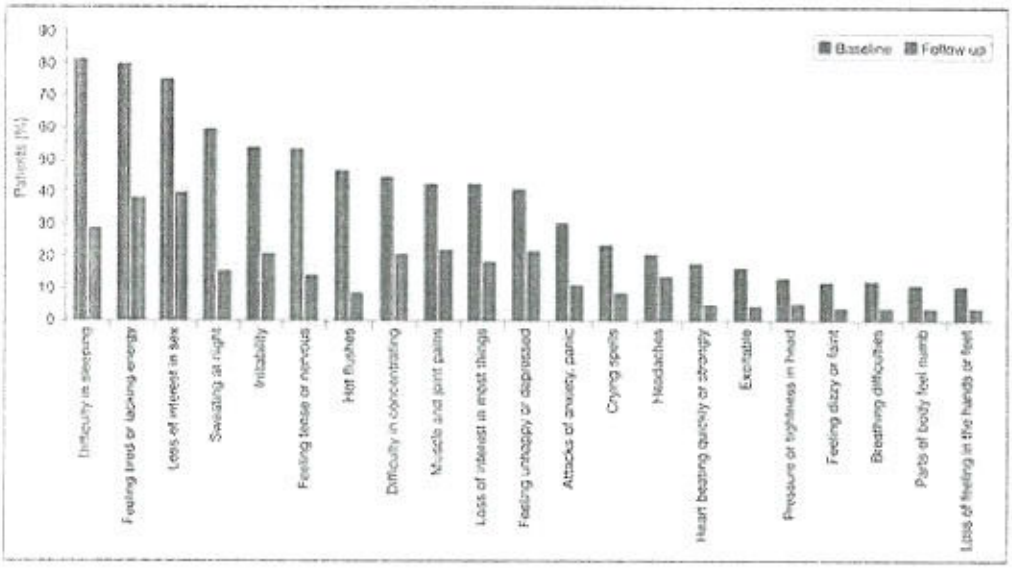

Figure 2. Changes in menopausal symptoms before and after BHRT. Bar chart expressing the percentage (%) of patients experiencing individual symptoms at the top 2 categories of the Likert scale (2 - Quite a bit and 3 - Extremely) before (baseline) and after BHRT treatment (follow-up). The 21 symptoms from the Greece Climacteric Scale are shown by order of prevalence.

Baseline = before BHRT treatment, Follow-up = after BHRT treatment.

All the 21 menopausal symptoms from the Greene Climacteric Scale are represented by order of prevalence. Results demonstrate that there is a significant decrease in symptom intensity for all the symptoms assessed after BHRT treatment. The t symptoms, represented by the symptoms that were experienced by 50% or more patients before starting BHRT treatment (baseline), were greatly reduced amongst patients after BHRT treatment (follow-up):

- Difficulty in sleeping which was experienced by 81% of the patients at baseline was present in only 29% of the patients at the time of follow-up (2.8-fold reduction)
- Feeling tired or lacking in energy improved from 80% of patients at baseline to 38% at follow-up (2.1-fold reduction)
- Loss of interest in sex improved from 75% of patients at baseline to 40% at follow-up (1.9-fold reduction)

- Sweating at night improved from 59% of patients at baseline to 15% at follow-up (3.9-fold reduction)
- Irritability improved from 54% of patients at baseline to 20% at follow-up (2.7-fold reduction)
- Feeling tense or nervous improved from 54% of patients at baseline to 14% at follow-up (3.9-fold reduction) (*Figure 2*).

The remaining symptoms have also all improved upon BHRT treatment: hot flushes (5.8-fold reduction), difficulty in concentrating (2.3-fold reduction), muscle and joint pains (2.0-fold reduction), loss of interest in most things (2.3-fold reduction), feeling unhappy or depressed (1.9-fold reduction), attacks of anxiety/panic (2.7-fold reduction), crying spells (2.9-fold reduction), headaches (1.4-fold reduction), heart beating quickly or strongly (3.4-fold reduction), excitable (5.3-fold reduction), pressure or tightness in head (2.6-fold reduction), feeling dizzy or faint (4-fold reduction), breathing difficulties (4-fold reduction), parts of body feel numb (3.3-fold reduction), and loss of feeling in hands or feet (3.3-fold reduction) (*Figure 2*).

Statistical analysis using a two-tailed, paired t-test was performed on the score values for the different menopausal symptoms before and after BHRT treatment. *Table 1* shows p-values, demonstrating that differences between baseline and follow-up are highly statistically significant for the majority of symptoms (*Table 1*).

Table 1. P-values demonstrating the statistical significance of changes in symptoms' intensity before and after BHRT

	Baseline		Follow-up		
	Mean	SEM	Mean	SEM	p-v
Difficulty in sleeping	2.1	0.103	1.1	0.108	<0.001
Feeling tired or lacking energy	2.2	0.107	1.3	0.107	<0.001
Loss of interest in sex	2.0	0.106	1.3	0.130	<0.001
Sweating at night	1.7	0.120	0.5	0.089	<0.001

	Baseline		Follow-up		
	Mean	SEM	Mean	SEM	p-value
Irritability	1.6	0.108	1.0	0.084	<0.001
Feeling tense or nervous	1.5	0.100	0.9	0.087	<0.001
Hot flushes	1.5	0.136	0.5	0.078	<0.001
Difficulty in concentrating	1.5	0.116	0.9	0.107	<0.001
Muscle and joint pains	1.4	0.113	0.8	0.096	<0.001
Loss of interest in most things	1.3	0.125	0.6	0.107	<0.001
Feeling unhappy or depressed	1.3	0.113	0.8	0.117	<0.001
Attacks of anxiety, panic	1.0	0.116	0.7	0.088	<0.01
Crying spells	1.0	0.108	0.5	0.089	<0.001
Headaches	0.8	0.104	0.6	0.097	<0.05
Heart beating quickly or strongly	0.7	0.095	0.3	0.068	<0.001
Excitable	0.7	0.093	0.4	0.069	<0
Pressure or tightness in head	0.6	0.100	0.2	0.065	<0.01
Feeling dizzy or faint	0.6	0.088	0.1	0.050	<0.001
Breathing difficulties	0.4	0.088	0.1	0.053	<0.001
Parts of body feel numb	0.4	0.093	0.2	0.060	*NS

	Baseline		Follow-up		
	Mean	SEM	Mean	SEM	p-value
Loss of feeling in the hands or feet	0.4	0.100	0.2	0.073	<0.05

Mean values and standard error of the mean (SEM) of the scores at baseline and follow-up, for all 21 symptoms.

*NS= not statistically significant.

View as image

Discussion

These data demonstrate that hormone balancing using compounded BHRT according to the local clinical guidelines improves QoL and menopause-associated symptoms in women experiencing symptoms of the menopause.

We used the Green Climacteric Scale consisting of 21 questions as a measurement tool of menopausal symptoms. This is a standardised QoL questionnaire specific to menopause that is well validated, ensuring consistent measurement and allowing for comparison of data across different studies. A lower score in the Green Climacteric Scale indicates a better QoL. BHRT treatment resulted in a 52% significant decrease in the Greene Climacteric Scale score, suggesting a 52% improvement in QoL. All 21 menopausal symptoms assessed were reduced greatly after BHRT treatment. The top six symptoms that were experienced by 50% or more of the patients before starting BHRT treatment included: difficulty in sleeping, feeling tired or lacking in energ of interest in sex, sweating at night, irritability and feeling tense or nervous. symptoms were reduced between 3.9- and 1.9-fold after BHRT treatment. The other symptoms that also significantly improved upon BHRT treatment were: hot flushes, difficulty in concentrating, muscle and joint pains, loss of interest in most things, feeling unhappy or depressed, attacks of anxiety/panic, crying spells, headaches, heart beating quickly or strongly, excitable, pressure or tightness in head, feeling dizzy or faint, breathing difficulties, parts of body feel numb, and loss of feeling in hands or feet. Although hot flushes were not part of the top symptoms, as they were experienced by only 46% of patients at baseline, this symptom reduced the most amongst all 21 symptoms, with a 5.8-fold reduction.

These data provide further insight into the efficacy of compounded BHRT in menopausal, symptomatic women, supporting previous studies where BHRT has been shown to improve QoL. A cross-sectional study on postmenopausal women showed that BHRT improved QoL, assessed by the Greene Climacteric Scale: women using micronized progesterone-containing HRT experienced a significant improvement in all three main symptom areas (vasomotor, physical and psychological), similar to what was observed in the study (**Fitzpatrick et al, 2000**). In the REPLENISH trial, women with moderate to severe vasomotor symptoms treated with BHRT (using a combination of estradiol and progesterone) reported a significant improvement in menopause-related QoL from baseline up to 12 months (**Simon et al, 2019**). Leonetti and colleagues also demonstrated, in a randomised controlled trial, that progesterone significantly improves vasomotor symptoms in menopausal women (**Leonetti et al, 1999**). These data correlate with the studies findings that BHRT improves QoL and results in a 3.9-fold and 5.8-fold reduction in the vasomotor symptoms sweating at night and hot flushes respectively, in women experiencing menopausal symptoms. Another study showed that compounded BHRT in varying regimens is effective in improving menopausal symptoms. Women experienced a 25% decrease in emotional lability, a 25% decrease in irritability, a 22% reduction in anxiety, a 14% reduction in night sweats and a 6% reduction in hot flashes within 3-6 months. Compounded BHRT allows for individualised preparations, which has been suggested to further improve effectiveness, safety, and tolerability of treatments (**Holtorf, 2009**; **Ruiz et al, 2011**).

Nonetheless, the number of studies in the literature assessing the role of BHRT, and particularly compounded BHRT, on QoL are scarce, which reinforces the importance of our findings in this present study. In addition, it is important to note that while most studies on BHRT use estradiol and progesterone only, our personalised treatment protocols can also incorporate testosterone and DHEA, contributing to a more physiological hormone balance, which may lead to better clinical outcomes.

This study is an observational retrospective one and therefore offers some limita
There was limited control over data collection, resulting in some inconsistency in terms of the timing of follow-up across patients. In addition, the study had a high discontinuation rate with over 300 patients completing the QoL questionnaire at baseline but only 69 patients completing the follow-up questionnaire, which limited the sample size of the study. Nevertheless, because of the immediate availability of the data, the small-scale pilot study provided a quick and reliable way to correlate BHRT based on the studies clinical protocols with QoL in women experiencing menopausal symptoms.

Conclusions

This study provided clinical evidence that hormone balancing using compounded BHRT according to the clinics local clinical guidelines is effective in reducing menopausal symptoms and improving QoL. In addition, these data pave the way for the implementation of a full-scale, larger prospective study, where researchers would aim to analyse data from a significantly larger number of women. In a future study, the MENQOL-Intervention would be used, which is currently the most validated and updated measurement scale for menopause, to assess QoL in menopausal women. The MENQOL-Intervention is a modified version of the MENQOL, which is particularly recommended for studies involving hormone replacement therapy. It contains additional questions relating to symptoms as a consequence of medical intervention, allowing for assessment of treatment safety and potential side-effects (**Lewis et al, 2005**).

Key Points

- Compounded BHRT improves quality of life by 52% and reduces menopause-associated symptoms in women
- All 21 menopause-associated symptoms assessed were significantly reduced after compounded BHRT treatment, including difficulty in sleeping, feeling tired or lacking in energy, loss of interest in sex, sweating at night, irritability, feeling tense or nervous, and hot flushes (between 5.8 and 1.9-fold reduction)
- Our study used the Greene Climacteric Scale, a standardised QoL questionnaire specific to menopausal symptoms, that is well established, validated and allows for comparison of data across different studies
- This is an observational retrospective small study that paves the way for our future full-scale study, where we aim to assess QoL and safety in a significantly number of women.

CPD reflective questions

- How does the increasing acknowledgment of the effects of menopause on women's health and QoL affect women's search for alternative treatment options, such as compounded BHRT?
- What are the main benefits of prescribing compounded BHRT compared to other forms of HRT?

- How can the use of different measurement scales for menopausal symptoms, such as the MENQOL-Intervention which are being implemented for future studies, affect final outcomes?