Efficacy and Tolerability of Compounded Bioidentical Hormone Replacement Therapy

Abstract

The primary purpose of this six-week survey study of women currently taking compounded bioidentical hormone replacement therapy was to determine if compounded bioidentical hormone replacement therapy relieves symptoms of menopause and is well tolerated. The secondary purpose of this study was to compare the symptom relief and tolerability of compounded bioidentical hormone replacement therapy to previously used commercially available products. All strengths and dosage forms of bi-estrogen and tri-estrogen were included, whether used alone or in combination with progesterone, dehydroepiandrosterone or testosterone. The survey instrument consisted of nineteen questions and evaluated the outcomes and side effects for commercially available versus compounded bioidentical hormones.

A total of 160 surveys was distributed and 78 were completed. Overall, 57.7% of the women surveyed reported fewer side effects and 71.8% of the women had better relief of menopausal symptoms when using bioidentical hormone replacement therapy. The occurrence and severity of menopausal symptoms decreased significantly after beginning bioidentical hormone replacement therapy. Before treatment, moderate-to-severe symptoms of hot flashes, night sweats, sleep problems, dry skin/hair, vaginal dryness, foggy thinking, mood swings and decrease in sex drive were reported in 52% to 70% of the women. After initiating treatment the moderate-to-severe range of symptoms dropped to between 4% and 20%. The most commonly reported side effects with bioidentical hormone replacement therapy were weight gain (37.2%), breast tenderness (19.2%) and bloating (23.1%). Weight gain (56.2%), breast tenderness (54.5%), bloating (40%) and mood swings (36.4%) were most commonly seen with commercially available products.

Bioidentical hormone replacement relieved the symptoms of menopause and was well tolerated.

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Introduction

The traditional theories that hormone replacement therapy (HRT) decreases the risk for heart disease and breast cancer in postmenopausal women have been refuted by recent publications. These results have left women searching for alternatives to traditional treatment. One option is bioidentical hormone replacement therapy (BHRT). Bioidentical hormones are derived from plant sources, such as soy and yams, and have precisely the same chemical structure as the hormones found in the human body. They include estrogen, progesterone, testosterone and dehydroepiandrosterone (DHEA). Bioidentical hormones appear to be equivalent to effects on endometrial stimulation when compared to synthetic hormones.[1] Although many healthcare professionals believe that bioidentical hormones are safe, few studies have established their safety or efficacy.[1]

The three forms of estrogen produced in the human body are estrone (E_1), estradiol (E_2) and estriol (E_3). The estrogen composition in the female body is approximately 3% estrone, 7% estradiol and 90% estriol.[2] The potencies of these hormones vary, with estradiol being the most potent followed by estrone and estriol. Estrogens are responsible for relieving menopausal symptoms, decreasing the risk of colorectal cancer and increasing bone density, leading to fewer osteoporotic fractures. Two estrogen formulations are commonly compounded: tri-estrogen (tri-est) and bi-estrogen (bi-est). Tri-est consists of estriol, estradiol and estrone in an 8:1:1 ratio, respectively. Bi-est contains only estriol and estradiol in a ratio of 8:2, respectively. Bi-est is occasionally used in a 9:1 ratio. Some practitioners prefer bi-est over tri-est because the estrone component is thought to be the most common estrogen associated with breast cancer.[1]

Progesterone is partly responsible for preventing osteoporosis and relieving hot flashes and other menopausal symptoms.[1] Micronized progesterone is composed of smaller particles that may aid in absorption.[1]

Many studies over the past decade have evaluated the effects of HRT in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, the first trial to compare bioidentical with synthetic hormones, concluded that treatment with conjugated equine estrogen in combination with medroxyprogesterone or micronized progesterone led to an increase in high-density lipoprotein (HDL), a decrease in low-density lipoprotein (LDL) and a decrease in fibrinogen. These results suggest a decrease in heart disease and stroke. The PEPI trial determined that micronized progesterone produced a higher HDL level than medroxyprogesterone, and that both provide protection from endometrial hyperplasia.[3]

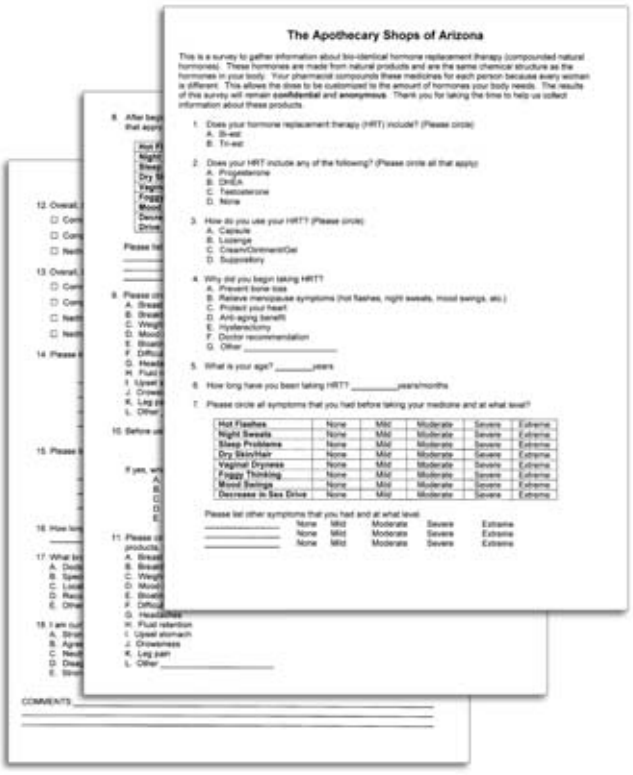
Additionally the Women's Health Initiative (WHI) trial studied the risks and benefits of using a combination estrogen/progestin to reduce the incidence of heart disease, breast and colorectal cancer and fractures in postmenopausal women. The results revealed an increased risk of heart disease and breast cancer; however, beneficial outcomes were seen with fractures and colorectal cancer.[2] The WHI trial was discontinued early when the risks were found to outweigh the benefits of treatment. The medications used in the WHI trial included conjugated equine estrogen (Premarin) or a combination product consisting of conjugated equine estrogen and medroxyprogesterone (Prempro). The conjugated equine estrogen arm of the study is still in progress.

The WHI trial did not evaluate quality of life or menopausal symptom relief. When the trial was discontinued early, many women with severe symptoms of menopause were left searching for alternatives to symptom relief. The primary outcome of this study is to determine if compounded bioidentical hormone replacement therapy (CBHRT) relieves symptoms of menopause and is well tolerated. Secondarily, these results will be compared to symptom relief and tolerability of commercially available products taken previously by the same patients.

Materials and Methods

A survey instrument (Figure 1) was developed to determine if CBHRT relieved the symptoms of menopause and was well tolerated. The survey instrument consisted of nineteen questions. Patients were asked which formulation of compounded estrogen they were taking, as well as any other hormones added to their formulation of estrogens. Options included progesterone (micronized), DHEA and testosterone. Patients also specified dosage form, including capsules, lozenges, creams/ointments/gels and suppositories. Reasons for initiating therapy were listed, with choices including prevention of bone loss, relief of menopausal symptoms, protection of the heart, anti-aging benefit, posthysterectomy and physician recommendation. Women were given the opportunity to add additional reasons for initiating HRT. The duration of therapy and age of patient were also requested.

Figure 1. Survey Instrument.



A downloadable copy of this survey is available at www.ijpc.com/hrtsurvey

Questions concerning menopausal symptoms before and after treatment included symptoms such as hot flashes, night sweats, sleep problems, dry skin/hair, vaginal dryness, foggy thinking, mood swings and a decrease in sex drive. Women were also given the opportunity to add additional symptoms they had experienced. Symptoms' severity and occurrence were rated on a scale of 1 to 5, with 1 being no symptoms and 5 being extreme symptoms. An identical question was asked for symptoms after initiating CBHRT. Patients were asked to indicate side effects experienced while taking CBHRT, including breast tenderness, breakthrough bleeding, weight gain, mood swings, bloating, difficulty sleeping, headaches, fluid retention, upset stomach, drowsiness and leg pain. Women were again given the opportunity to record additional side effects they may have experienced.

Also, women were asked if they had used commercially available products prior to beginning CBHRT. Similar questions were asked regarding side effects of commercially available products. Several products were listed as choices, including Premarin, Provera, Prempro, Premphase, Estrace or estradiol, Cenestin, Ogen and Prometrium, with the option to include

Table 1. Severity and Occurrence of Symptoms Before Taking Hormone Replacement Therapy.

Symptom	*None (%)*	*Mild (%)*	*Moderate (%)*	*Severe (%)*	*Extreme (%)*
Hot flashes	15.58	14.58	28.57	31.17	10.39
Night sweats	25.97	15.58	20.78	27.27	10.39
Sleep problems	20.78	16.88	23.38	28.57	10.39
Dry skin/hair	36.36	22.08	25.97	14.29	1.3
Vaginal dryness	24.68	23.38	29.87	15.58	6.49
Foggy thinking	36.36	11.69	37.66	9.09	5.19
Mood swings	32.89	11.84	30.26	19.74	5.26
Decrease in sex drive	30.26	17.11	28.95	15.79	7.89

Table 2. Severity and Occurrence of Symptoms After Taking Compounded Bioidentical Hormones.

Symptom	*None (%)*	*Mild (%)*	*Moderate (%)*	*Severe (%)*	*Extreme (%)*
Hot flashes	72.22	23.61	2.78	1.39	0
Night sweats	68.06	23.61	6.94	1.39	0
Sleep problems	58.33	23.61	15.28	2.78	0
Dry skin/hair	54.17	30.56	13.89	1.39	0
Vaginal dryness	55.56	30.56	9.72	4.17	0
Foggy thinking	55.56	29.17	13.89	1.39	0
Mood swings	60.56	32.39	5.63	1.41	0
Decrease in sex drive	50.00	29.17	9.72	6.94	4.17

additional commercially available products. The survey included questions to evaluate the relief of menopausal symptoms and side effects for CBHRT versus commercially available products. Participants were further asked to list other concurrent medications and over-the-counter medications used while taking HRT and to indicate any side effects experienced with these products. In addition, patients were asked about their satisfaction with the pharmacy, the length of time they had been a customer and how they were referred to the pharmacy.

Patients were recruited for the study at three independently owned compounding pharmacies. Women picking up or dropping off prescriptions for compounded bioidentical hormones were asked to participate in the study. Surveys were distributed over a six-week period. To maintain confidentiality the surveys were distributed by pharmacy personnel with a request that the surveys be returned in a blank envelope. The primary investigator did not distribute or accept any surveys. Patients were included in the study if they were taking any dosage form of bi-est or tri-est alone or in combination with progesterone (micronized), testosterone or DHEA. Dosage forms included were topical creams, lozenges, capsules, sublingual drops, vaginal creams/gels or suppositories. A total of 160 surveys was distributed over the six-week period.

Statistics

Statistical analysis was conducted using SAS (Cary, North Carolina) Statistical Software 8.2. Descriptive statistics were conducted on all variables in the survey and paired *t*-tests were used to compare measurements prior to and after CBHRT was taken. Correlations were also conducted to determine any relationships that may exist between survey variables and demographic information provided. An a priori α=0.05 was set.

Results

A total of 160 surveys was distributed and 78 surveys were completed over the six-week period (49% response rate). Of the 78 surveys received 62 (79.5%) patients were taking bi-est and 16 (20.5%) patients were taking tri-est. In addition to the estrogen, 59 patients were taking progesterone (micronized), 4 patients were taking DHEA and 12 patients were taking testosterone. Sixty-five patients used capsules; 8 used lozenges; 6 used creams, ointments or gels; 1 used suppositories; and 1 used sublingual drops. The mean age of women completing the survey was 53.8 years old and on average women had been taking HRT for 73.8 months.

The most common reason for initiating HRT was to relieve menopausal symptoms (73%), to prevent bone loss (31%), being posthysterectomy (28.3%), for anti-aging benefit (23%) and to protect the heart (17.9%). Other reasons for initiating HRT included better sleep, excessive bleeding and to be as healthy as possible.

Severity and occurrence of symptoms with compounded bioidentical hormones are reported in Tables 1 and 2. Before treatment, moderate-to-extreme symptoms of hot flashes and night sweats were approximately 70% and 60%,

Table 3. Comparison of Occurrence and Severity of Symptoms.

Symptom	*Symptoms before taking medication (Mean ± SD)*	*Symptoms after using CBHRT (Mean ± SD)*	t *value*	*p value*
Hot flashes	3.1 ± 1.2	1.3 ± 0.6	13.52	<.0001
Night sweats	2.8 ± 1.4	1.4 ± 0.7	9.51	<.0001
Sleep problems	2.9 ± 1.3	1.6 ± 0.8	8.79	<.0001
Dry skin/hair	2.2 ± 1.1	1.6 ± 0.8	5.89	<.0001
Vaginal dryness	2.6 ± 1.2	1.6 ± 0.8	7.21	<.0001
Foggy thinking	2.4 ± 1.2	1.6 ± 0.8	6.34	<.0001
Mood swings	2.5 ± 1.3	1.5 ± 0.7	8.17	<.0001
Decrease in sex drive	2.5 ± 1.3	1.9 ± 1.1	4.21	<.0001

Note: For statistical evaluation, none = 1, mild = 2, moderate = 3, severe = 4 and extreme = 5.
CBHRT = compounded bioidentical hormone replacement therapy
SD = standard deviation

respectively. After initiating CBHRT, the number of patients with symptoms dropped to roughly 4% and 8%, respectively. Before treatment, moderate-to-extreme symptoms of sleep problems, dry skin/hair and vaginal dryness were approximately 62%, 42% and 52%, respectively. After initiating CBHRT, the number of patients with symptoms dropped to roughly 18%, 15% and 14%, respectively. Before treatment, moderate-to-extreme symptoms of foggy thinking, mood swings and a decrease in sex drive were approximately 52%, 55% and 53%, respectively. After initiating CBHRT, the numbers decreased to 15%, 7% and 20%, respectively. In addition to the symptoms listed, women also reported depression, anxiety, leg aches, stress incontinence, memory issues, breast tenderness, osteoporosis, facial hair growth, hair loss, dizziness, weight gain, exhaustion, sensitivity to heat, cramps, heart palpitations and headaches. With respect to severity, Table 3 shows that each individual symptom was significantly lessened after beginning CBHRT. Using the scale of 1 (experiencing no symptoms) and 5 (experiencing extreme symptoms), hot flashes declined from a mean of 3.1 to mean of 1.3, night sweats (2.8 to 1.4), sleep problems (2.9 to 1.6), dry skin/hair (2.2 to 1.6), vaginal dryness (2.6 to 1.6), foggy thinking (2.4 to 1.2), mood swings (2.5 to 1.5) and decrease in sex drive (2.5 to 1.9). A correlation was found between the mean sum of symptom severity before treatment with HRT (20.9) and the mean sum of symptom severity after treatment with CBHRT (12.5).

With respect to side effects, women taking CBHRT most commonly reported weight gain (37.2%), breast tenderness (19.2%) and bloating (23.1%). Side effects reported with commercially available products were similar but at a higher occurrence. Weight gain (56.2%), breast tenderness (54.5%), bloating (40%) and mood swings (36.4%) were most commonly reported with commercially available products. As a whole, women using bioidentical hormones experienced a lower percentage of side effects (Table 4). In addition to the side effects listed, one woman in the bioidentical group had excessive bleeding. Women using commercially available hormones reported feeling terrible, having breast lumps (needing surgery), being depressed, having difficulty concentrating, feeling extreme heat sensitivity, having fibrocystic breasts, feeling fatigue, having muscular tension, having pancreas pain and having gastritis.

Table 4. Compounded Bioidentical Hormones versus Commercially Available Hormones: Side Effects.

Overall, I feel I had fewer side effects with commercially available products.	2.6%
Overall, I feel I had fewer side effects with bioidentical hormones.	57.7%
Neither, I experienced the same amount of side effects with both.	39.7%

Table 5. Compounded Bioidentical Hormones versus Commercially Available Hormones: Menopausal Symptoms.

Overall, I feel I had better relief of my menopausal symptoms with commercially available products.	2.6%
Overall, I feel I had better relief of my menopausal symptoms with bioidentical hormones.	71.8%
Neither, I had the same amount of relief with both.	12.8%
Neither, I had no relief with either.	12.8%

Fifty-five women had used commercially available products prior to beginning CBHRT, allowing comparisons to be made between the commercially available products and CBHRT. Overall, 57.7% of women reported fewer side effects when using compounded bioidentical hormones (Table 5). Conversely, 2.6% reported fewer side effects when using commercially available products and 40% reported that they experienced the

Table 6. Side Effect Comparison of Compounded Bioidentical Hormones and Commercially Available Hormones.

Symptom	*Compounded bioidentical hormones (n = 78)*	*Commercially available hormones (n = 55)*
Breast tenderness	15 (19.2%)	30 (54.5%)
Breakthrough bleeding	13 (16.6%)	13 (23.6%)
Weight gain	29 (37.2%)	31 (56.4%)
Mood swings	4 (5.1%)	20 (36.4%)
Bloating	18 (23.1%)	22 (40%)
Difficulty sleeping	13 (16.6%)	19 (30.1%)
Headaches	5 (6.4%)	15 (27.3%)
Fluid retention	12 (15.4%)	17 (30.1%)
Upset stomach	3 (3.8%)	6 (11%)
Drowsiness	5 (6.4%)	3 (5.5%)
Leg pain	4 (5.1%)	6 (11%)

same amount of relief with both. Overall, 71.8% of women reported better relief of their menopausal symptoms when using compounded bioidentical hormones. Conversely, 2.6% reported better relief with commercially available products, 12.8% reported they had the same amount of relief with both and 12.8% reported they had no relief with either. Table 6 shows a comparison of the most commonly reported side effects of the compounded bioidentical hormones and the commercially available hormones.

Women reported taking over-the-counter and herbal products as well as prescription medications for asthma, allergies, thyroid disorders, osteoporosis and hypertension. Additionally,

3 women reported concurrently using estradiol (Estrace); 8 women reported using selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine (Prozac), paroxetine (Paxil), escitalopram (Lexapro), citalopram (Celexa) and sertraline (Zoloft); 2 women reported using amitriptyline (Elavil); and 1 reported using buproprion (Wellbutrin). Women also reported concurrent use of over-the-counter and herbal products. One woman reported using Estroven, 3 reported using evening primrose, 1 reported using black cohosh and 4 reported using DHEA. In addition multivitamins, vitamin C, vitamin E, vitamin B complex and calcium were also reported as used. Women concurrently using these medications that may have affected menopausal symptoms could have responded differently to survey questions. Consequently, *t*-tests and chi square analyses were conducted between those that reported concurrent medication use and those who did not. Statistical analyses indicated that no significant differences existed between the two groups. As a result these responders were included in the study.

Discussion

Few studies have been completed to establish whether CBHRT relieves menopausal symptoms or is well tolerated. The information revealed in this study is valuable for recommending HRT to women seeking menopausal symptom relief. Women taking bioidentical hormones reported a statistically significant decrease in symptom severity from baseline. The severity and occurrence of menopausal symptoms decreased in the majority of women using bioidentical hormones, in most cases dropping to the *none*, *mild* or *moderate* category. The greatest reduction in symptom severity after initiating CBHRT was observed as a reduction in hot flashes and night sweats. Furthermore it was noted that women taking CBHRT had a significant decrease in the severe and extreme ranges for all symptoms. Although the decrease in symptom severity for libido produced the least amount of change, the severity was reduced by one third in women using CBHRT. This may indicate that a decrease in libido may require a more specific treatment. These results are encouraging for women with moderate-to-severe menopausal symptoms and quality-of-life issues.

Often when one takes medications, the side effects can be as debilitating as the symptoms of the condition. Some side effects were observed in women taking CBHRT as well as with commercially available products. However, women using compounded bioidentical hormones experienced fewer side effects when compared with prior use of commercially available products. The most commonly reported side effects in both groups included breast tenderness, weight gain and bloating. In addition, when using commercially available products, a large percentage of women experience mood swings. This result was not observed with bioidentical hormones. Overall, the majority of women reported fewer side effects and better relief of menopausal symptoms when using compounded bioidentical hormones versus commercially available products. These results are beneficial for women who cannot tolerate or have failed therapy with commercially available products and provide them with many opportunities when seeking alternatives to commercially available products.

The mean age of a woman in menopause is 51 years, ranging from 45 to 55 years.[4] The mean age of women who completed the survey involved in this study was 53.8 years. The mean duration of treatment with HRT was 73.8 months, signifying that in this study population the mean age that women initiated HRT was 47.7 years. Both the mean age of women initiating HRT and the mean age of participants completing the survey are within the established range of menopause. This correlates with the finding that 73% of women who completed the survey initiated HRT to relieve the symptoms of menopause. This collection of data supports the assumption that the sample size for this survey study was accurately chosen for females in menopause.

To determine if the women involved in this study were taking any other medications that may have synergistically influenced the outcomes of the study, the participants were asked if they were taking any other prescription, over-the-counter medications or herbal products concurrently. Some of the prescription medications reported, specifically the SSRIs, may have influenced the symptoms of menopause. The medications with effects on serotonin may play a part in relieving hot flashes and mood disorders. A few over-the-counter medications may have also contributed to the relief of menopausal symptoms. These products include Estroven, black cohosh, evening primrose and DHEA. A total of 23 women were taking prescription or over-the-counter medications which may have synergistically affected the outcomes of the study. These women were not excluded as statistical analyses showed no statistical difference between those who were using concurrent medications and those who were not.

With the current data relating to the risks and benefits of HRT, making recommendations for treatment is not as easy as it once was. Presently, the primary reason women are seeking treatment with HRT is to relieve the symptoms of menopause and improve quality of life. It is not recommended that women with a history of breast cancer or heart disease use HRT. Every woman and situation should be examined on an individual basis to assess the risks and benefits of HRT. Candidates for HRT may include those with no history of coronary heart disease or breast cancer and those who have moderate-to-severe menopausal symptoms or are at risk for colorectal cancer or osteoporosis. Each patient is unique, and treatment should be assessed accordingly. With the current result from the WHI trial, it was interesting to find that 17.9% of women initiated HRT to protect the heart. These women may have initiated therapy before the negative results were revealed[1] or the results may have influenced their decision to switch to CBHRT.

While the results of this study suggest that CBHRT provides an efficacious and useful role in symptom management in

post-menopausal women, a few limitations should be addressed. First, women may have initiated CBHRT because they did not tolerate commercially available products or they were not effective. Additionally, the survey was given only to women who were taking CBHRT; women who were taking commercially available products were not surveyed separately. Women were asked if they had previously taken commercial products, and these results were compared to those with CBHRT. The result of this study may have been different if women had switched from CBHRT to commercially available products. Another limitation was that the survey was handed out in the pharmacy lobby, introducing selection bias. Biases may have been reduced if the surveys were mailed to all women taking any form of HRT. A third limitation is that only patients of selected compounding pharmacies were asked to fill out the survey. It is unclear if the results would have been different if the survey had been distributed to more traditional dispensing pharmacies. More studies need to be conducted to compare compounded bioidentical hormones and commercially available products. The next step in this process would be to use a similar instrument to survey patients taking commercially available products separately from those taking compounded bioidentical hormones.

Conclusion

While this study does not prove that compounded bioidentical hormones are safer than commercially available products, it does show that compounded bioidentical hormones are well received, relieve the symptoms of menopause and are well tolerated. Future studies should be conducted prospectively to identify the exact benefits and side effects of CBHRT, so that CBHRT can be appropriately and effectively utilized in postmenopausal women.

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