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NAMS Survey

Use of compounded hormone therapy in the United States: report of The North American Menopause Society Survey

Abstract

Objective: A national survey was conducted to determine the extent of use of compounded hormone therapy (C-HT) and to characterize the differences between C-HT users and users of hormone therapy approved by the US Food and Drug Administration (FDA-HT users).

Methods: This Internet survey enrolled 3,725 women aged 40 to 84 years who were postmenopausal or experiencing the menopause transition. The sample was weighted slightly by age, region, education, and race to reflect population attributes based on US Census data.

Results: Overall, 9% of women were current users of HT, and 28% of all respondents were ever-users of HT. C-HT users represented 31% of ever-users of HT, 35% of current users of HT, and 41% of ever-users aged 40 to 49 years. Approximately 13% of ever-users indicated current or past use of testosterone. The most cited reason for using HT was vasomotor symptoms (~70%). Nonapproved indications for using HT were selected more often by C-HT users. There were four reports of endometrial cancer among the 326 C-HT users compared with none reported among the 738 FDA-HT users. Significance was not determined because of small numbers.

Conclusions: This survey indicates substantial use of C-HT across the country and the possibility of higher rates of endometrial side effects with such products. There is a need for standardized data collection on the extent of use of compounded hormones and their potential risks.

Key Words: Bioidentical – Compounded hormone therapy – FDA – Testosterone.

The history of hormone therapy (HT) for treatment of menopausal symptoms is distinguished by periods of high use interspersed with periods of avoidance. During the recent peak, an estimated 21.6% of women aged 50 years and older used HT in the year 2000.[1] At that time, HT was believed to prevent several chronic conditions associated with aging in addition to alleviating menopausal symptoms. Conjugated equine estrogens were the most commonly prescribed HT in the United States and for some years the number one selling drug in the country. In 2002, a precipitous drop in the use of US Food and Drug Administration-approved HT (FDA-HT) followed the announcement of results from the estrogen-progestogen arm of the Women's Health Initiative (WHI).[2-4] The study reported an increased risk of coronary heart disease, stroke, venous thromboembolic disease, and breast cancer in the hormone users.[5]

Although subsequent analyses of WHI data support a favorable risk-benefit profile for HT use in healthy women who start therapy when aged younger than 60 years,[6] the initial perception that FDA-HT was unsafe opened the door for alternative therapies. In addition to many over-the-counter supplements, compounded hormones were aggressively marketed, typically promoted as being natural, safe, and "bioidentical."

Terminology associated with compounded hormones varies. Some of the terms are *bioidentical hormone therapy*,

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This survey was developed by The North American Menopause Society (NAMS) Advisory Panel consisting of representatives of the NAMS Board of Trustees and other experts in women's health: Margery L.S. Gass, MD, NCMP,[1] Cynthia A. Stuenkel, MD, NCMP,[2] Wulf H. Utian, MD, PhD, DSc(Med), [1] Andrea LaCroix, NCMP, PhD,[3] James H. Liu, MD,[4] Jan L. Shifren, MD, NCMP[5]

From the [1]North American Menopause Society, Mayfield Heights, OH; [2]Endocrinology and Metabolism Service, University of California, San Diego, School of Medicine; [3]Division of Epidemiology, University of California, San Diego, School of Medicine; [4]Department of Obstetrics and Gynecology, University Hospitals Case Medical Center, Cleveland, OH; and [5]Department of Obstetrics, Gynecology, and Reproductive Biology, Harvard Medical School, Boston, MA.

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Address correspondence to: The North American Menopause Society, 5900 Landerbrook Dr, Suite 390, Mayfield Heights, OH 44124. E-mail: info@menopause.org

bioidenticals, *compounded hormones*, *custom-compounded hormones*, and *compounded bioidentical hormone replacement therapy*. Because the term *bioidentical* is misleading and in current usage can refer to both compounded and certain preparations of FDA-HT, and because the FDA does not use the word *replacement*, we have chosen to use the term *compounded hormone therapy* (C-HT) in this publication.

The term *bioidentical* is defined as "having the same molecular structure as a substance produced in the body."[7] Chemical analyses, however, indicate that compounded bioidentical hormone products are not exactly the same as those physiologically produced because many isomers are created in the laboratory production process that do not match those in the body.[8] Some, including the FDA, have advocated avoiding use of the term because of the misleading connotation.[8] The FDA has determined that the term *bioidentical* is a marketing term and not a term of scientific or medical merit.[9]

Use of the word *natural* is also misleading because the word means that a product can be used as it is found in nature. Producing compounded estrogen requires a minimum of 15 chemical reactions in a laboratory, yielding an end-product that is no longer "natural," even if the original source is plant-based.[8] In addition, there are opportunities for unrecognized errors in production of C-HT products because FDA oversight is lacking.[10]

Unlike FDA-approved prescription drugs, prescribing and postmarketing surveillance data on compounded drugs are not tracked and available for review until a significant problem arises.[11,12] Because regulation of pharmaceutical compounding occurs on the state level, little is known about the extent of use and the magnitude of harm associated with C-HT. There is general consensus that the extent of use has grown here and elsewhere, perhaps beyond the bounds of accepted compounding practice.[13-16] The increase is due in part to website promotions, *New York Times* best-selling books on this topic, and unprecedented celebrity endorsements via media that reach millions of women.[17-20]

Because of the uncertainties surrounding C-HT, all relevant medical societies, including the American Association of Clinical Endocrinologists, the American Congress of Obstetricians and Gynecologists, the American Medical Association, the American Society for Reproductive Medicine, The Endocrine Society, The North American Menopause Society, the US Preventive Services Task Force, and the American College of Clinical Pharmacy, caution against the use of C-HT.[21-28] Nevertheless, the clinical impression is that use is rising, and quantification of use is challenging in the absence of mechanisms to track compounding pharmacy prescriptions and outcomes of C-HT product use.

In response to the paucity of information about C-HT use, The North American Menopause Society conducted an Internet-based consumer survey to assess the extent of C-HT prescribing and to characterize the C-HT population in terms of demographics, motivations, and outcomes. The participant age range of 40 to 84 years was intentionally broad to capture both menopausal and antiaging justification for using HT.

METHODS

Survey design

This survey was designed to collect information from US women about the use of C-HT. The survey was developed by an editorial panel composed of experts in the field of hormone therapy. The panel collaborated on survey content by means of conference calls and e-mails. Lake Research Partners provided research survey expertise and formatting to the final version of the survey.

Eligibility criteria included women aged from 40 to 84 years who were postmenopausal or who were currently going through the menopause transition. Women who reported no bleeding for 1 year or longer or reported having both ovaries removed were considered to be postmenopausal.[29] Going through the menopause transition was defined as not meeting the criteria for being postmenopausal but having irregular menses or menopausal symptoms such as hot flashes. Exclusion criteria included male sex or not meeting criteria defining menopausal status.

Survey administration

The survey was administrated online through Lake Research Partners, January 5-15, 2015, and January 29 to February 4, 2015. The sample was drawn from an online opt-in panel, recruiting respondents by e-mail invitation, and affiliate online networks offering respondents opportunity for rewards (such as cash, points, or sweepstakes entry) for survey completion. Of the 156,240 women invited to participate, 22,105 accepted, and 3,725 women were eligible (Fig. 1). The sample was weighted slightly by age, region, education, and race to reflect the population attributes based on US Census data. The margin of error for the total sample is $\pm 1.6\%$. The margin of error for the women who have taken/currently take hormones is $\pm 3.0\%$ and for the women in the C-HT group $\pm 5.4\%$.

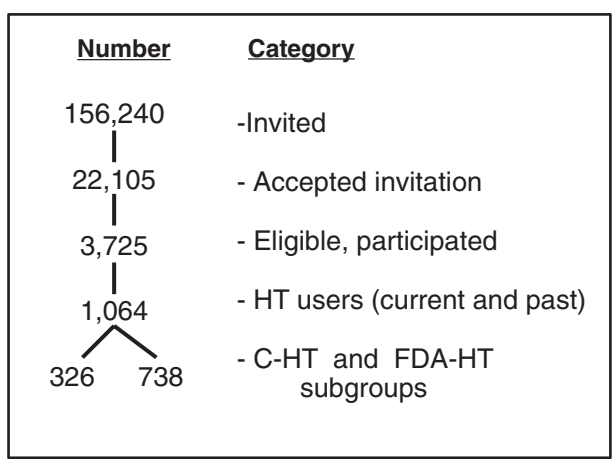

FIG. 1. Survey enrollment and participant categories.
C-HT, compounded hormone therapy; FDA-HT, US Food and Drug Administration-approved hormone therapy; HT, hormone therapy.

Survey interpretation

The express purpose of this survey was to acquire information from women about the use of C-HT compared with FDA-HT. As previous surveys have reported, women do not always know whether they are using C-HT, nor do they necessarily know whether the HT they use is approved by the FDA.[14] Distinguishing C-HT users from the women taking FDA-HT required that a) HT users identify themselves by response to a direct question about C-HT use or b) participants be categorized by their responses to questions that contain commonly accepted characteristics of C-HT use.

Women in this study were classified as being "presumed C-HT users" if they responded affirmatively to the specific question about C-HT use or if they indicated that they were unsure but responded elsewhere that they used saliva testing; used hormones by means of lozenges, pellets, or injections in muscle; used estriol, estrone, human chorionic gonadotropin (hCG), dehydroepiandrosterone (DHEA), or testosterone; answered no to whether the HT was approved by the FDA; answered yes to whether hormones were mixed specifically for them; or indicated that their hormones were prescribed by an antiaging doctor. Although injections of FDA-approved estrogen preparations were used in the past, for the purpose of this survey, injections were considered likely to be C-HT. Use of testosterone was considered to be use of C-HT because there is no FDA-approved testosterone product for women. Clinicians who treat women with testosterone prescribe either compounded testosterone (pellets, injections, creams, gels) or testosterone products FDA-approved for males with off-label dosing specified. Because female dosing for the FDA-approved male testosterone products has been neither tested nor approved, all testosterone use was classified as C-HT.

Statistical analysis

Chi-square tests and pairwise comparisons were performed on variables of interest. Pairwise comparisons were adjusted using the Bonferroni correction and a two-sided test of equality for column proportions. The variables that differed significantly from each other at the 0.05 level are indicated in the tables and text. Reporting significance levels was used sparingly and with caution because of small numbers in some cells.

RESULTS

Enrollment in the survey and distribution of primary subgroups are outlined in Figure 1. The response rate was 14%. Of those, 17% were eligible for the survey. Results for testosterone users are reported as a subset of the C-HT users.

Demographics

The sample reflected the US population of women aged between 40 and 84 years with respect to age, region, and race distribution (Table 1). Approximately one-third of the respondents had a college degree or postgraduate study. More than half (53%) of the participants had an income of more than $50,000. The majority of women were postmenopausal, but 33% indicated that they were in the menopause transition.[29] Three-fourths of the women reported current or past history of menopausal symptoms.

TABLE 1. *Participant demographics, expressed as percentages*

	Total cohort (n = 3,725)	C-HT (n = 326)	FDA-HT (n = 738)
Age, y			
40-49	28	28	18
50-59	32	29	23
60-69	26	28	40
70-84	15	14	19
Region			
Northeast	19	16	16
Midwest	21	17	18
South	38	44	43
West	22	23	24
Race			
White	62	62	66
Black	12	11	14
Latino	12	13	9
Asian-Pacific	8	5	6
Native American	2	2	2
Other	4	7	4
Income			
Below 50k	44	41	36
Above 50k	53	55	60
Unsure	3	4	3
Education			
Non-college graduate	68	67	66
College graduate, postgraduate	32	32	34

Both hormone user groups contain current and past users. Percentages may not total 100% because of rounding.
C-HT, compounded hormone therapy; FDA-HT, US Food and Drug Administration-approved hormone therapy.

Hormone therapy use

In this survey, approximately 28% of all respondents were ever-users of HT. Among the ever-users, 32% reported current use (9% of women surveyed). Percentages of women in each age group reporting current HT use were: 12% aged 40 to 49 years, 9% aged 50 to 64 years, 8% aged 65 to 74 years, and 5% aged 75 to 84 years. The majority (79%) of current users were aged 40 to 64 years. Women aged 65 to 74 years represented 16% of current users of HT, and women aged 75 to 84 years represented 5% of current users.

Women who use/used HT were slightly more likely to have an income of more than $50,000 (59% vs 51%), but there was no apparent difference in usage rates by education level. The percentage of women who used HT differed by region of the country. Of the four geographic regions used in the US Census, the South represents the highest percentage of the population (~38%)[30] and an even higher percentage (44%) of HT ever-users in the survey (Table 1).

Although only 29% of women had undergone a hysterectomy, they represented more than half of all HT users (51%). Of the women who had undergone a hysterectomy, 88% had had the surgery before menopause, and 62% reported that both ovaries were removed. Menopausal symptoms were reported at a slightly higher rate among HT users than among women in the entire cohort (Table 2).

TABLE 2. *Characteristics of participants, expressed as percentages*

Characteristic	Total cohort (n = 3,725)	C-HT (n = 326)	FDA-HT (n = 738)
Had hysterectomy	29	41	55[a]
Had/Has menopausal symptoms	76	86	81
Current hormone use	9	36	30
Past hormone use	19	64	70
Received HT risk/benefit information	76	75	76

Both hormone user groups contain current and past users.
C-HT, compounded hormone therapy; FDA-HT, US Food and Drug Administration-approved hormone therapy.
[a]$P < 0.05$, C-HT vs FDA-HT.

C-HT use versus FDA-HT use

Classification of users and extent of use. Women who used hormones were asked to indicate all of the hormones that they use/used from a generic list of hormones that included estrogen, progesterone, estradiol, testosterone, DHEA, estriol, hCG, estrone, growth hormone, and androstenedione. The majority of women reported using estrogen/estradiol with or without progesterone, and 6% or less of all C-HT users indicated use of DHEA, estriol, hCG, or estrone. However, 13% of women using HT reported use of testosterone, and 11% indicated that they were not sure what hormones they use/used (data not shown). Selection of testosterone, DHEA, estriol, hCG, or estrone was used to classify women as C-HT users.

Respondents were asked to select all the modes of delivery they used (Table 3). Several modes of HT delivery (muscle injections, pellets, and lozenges) were used to classify women as C-HT users. Only 2% of all hormone users indicated that they use/used hormones injected into the muscle. Percentages of users were approximately the same between the two HT groups with regard to skin patch, cream in vagina, tablets in vagina, and ring in vagina. However, oral pill use was selected by 77% of FDA-HT users and only 65% of C-HT users, whereas cream, lotion, or gel on skin was selected by 19% of C-HT users and only 5% of FDA-HT users (Table 3).

TABLE 3. *Modes of hormone delivery, expressed as percentages*

Mode of delivery	C-HT users (n = 326)	FDA-HT users (n = 738)
Pill form by mouth	65	77[a]
Cream, lotion, or gel on skin	19	5[a]
Skin patch	11	12
Cream in the vagina	8	9
Tablets in the vagina	3	3
Ring in the vagina	2	2
Spray on skin	2	0[a]
Injection in muscle[b]	5	0
Pellet inserted under skin[b]	2	0
Lozenge under tongue or near gums[b]	2	0
Other	3	3
Not sure	4	1[a]

Both hormone-user groups contain current and past users. Participants were asked to check all that apply.
C-HT, compounded hormone therapy; FDA-HT, US Food and Drug Administration-approved hormone therapy.
[a]$P < 0.05$, C-HT vs FDA-HT.
[b]Classifying characteristic, statistical analysis not applied.

Almost one-third of the women were not sure whether the hormones they were taking were approved by the FDA (Table 4). If participants were uncertain about the FDA-approval status of their HT, they were given the following information: "FDA approved hormones have a brand name like Premarin, Vagifem, Estrace, Vivelle dot, Prometrium, and others, while compounded hormones are identified by generic terms like estrogen, estrone, or progesterone." With the additional information, the rate of "unsure" responses decreased from 31% to 22%, at which point 80% of presumed FDA-HT users indicated that they thought their HT was FDA approved.

Women using saliva testing were presumed to be users of C-HT. Among all HT users, 5% indicated that they use/used saliva testing, and 6% were unsure. When asked how frequently they used saliva testing, users responded: daily, 9%; weekly, 2%; monthly, 17%; couple times per year, 14%; yearly, 35%; and not sure, 24%.

Applying all of the above information, it was estimated that among all current and past HT users, the rate of C-HT use was 31%. Among current users, the rate is approximately 35%.

Characteristics of users. The C-HT users tended to be younger than the FDA-HT users (Fig. 2). They were more likely to be going through the menopause transition, to have symptoms, and to be current hormone users at a time when C-HT was more widely available. FDA-HT users were more likely to be past users. A notable difference in hormone product use between current and past users is that 38% of current users selected *estradiol* as their estrogen product, but this was selected by only 11% of past users, who were more likely to select *estrogen* (58%). This finding suggests bioidentical terminology recognition by current users.

FDA-HT users had a higher rate of hysterectomy overall, although both C-HT and FDA-HT users had similar rates of having undergone hysterectomy before menopause (~92%) and similar rates of bilateral oophorectomy (~74%). The two groups of HT users reported similar rates of having received

TABLE 4. *Awareness of hormone therapy US Food and Drug Administration approval status before and after prompting, expressed as percentage*

FDA status	C-HT (n = 326)	FDA-HT (n = 738)
Before prompting		
FDA approved	46	71
Not FDA approved	5	0
Some are, some are not	14	0
Not sure	34	29
After prompting		
FDA approved	46	80
Not FDA approved	13	0
Some are, some are not	13	0
Not sure	29	20

Both hormone user groups contain current and past users. Prompting included a few examples of commonly used, FDA-approved, brand name hormones. Percentages may not total 100% because of rounding.
C-HT, compounded hormone therapy; FDA-HT, US Food and Drug Administration-approved hormone therapy.

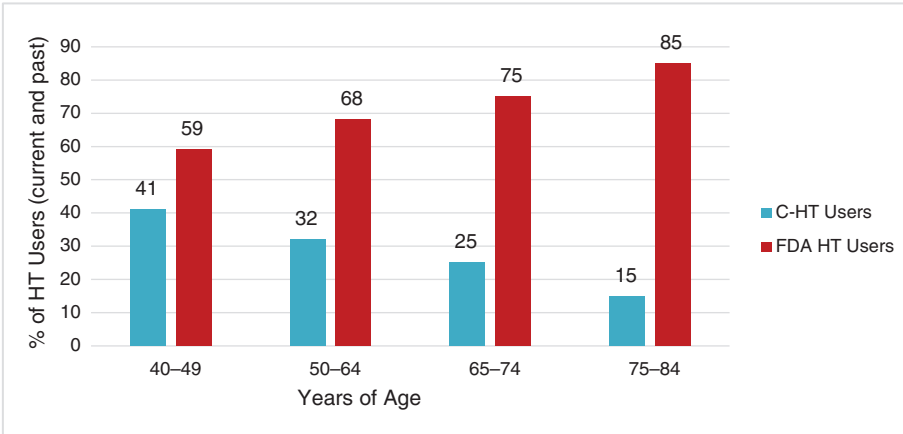

FIG. 2. Percentage of all HT users in four age groups using C-HT or FDA-HT.
C-HT, compounded hormone therapy; FDA-HT, US Food and Drug Administration-approved hormone therapy; HT, hormone therapy.

information about benefits and risks of HT from their providers (Table 2).

Participants were asked whether they thought that "natural" or "bioidentical" hormones are safer than other types of hormones. More C-HT users (42%) than FDA-HT users (25%) believed that such hormones are safer ($P < 0.05$) (Table 5).

Indications for use. The main reason women used HT was to treat vasomotor symptoms (VMS) (Table 6). Although 70% of each HT group selected treating VMS as a reason for use, all of 13 potential reasons for using HT included in the survey were selected to varying degrees by both groups. Two other approved indications for using HT—treating vaginal dryness and preventing osteoporosis—along with treating moodiness and irritability (not an approved indication) were selected by 24% to 27% of all hormone users. Additional indications not approved for HT were selected more often by the C-HT users. These included improving moodiness or irritability, sleep problems, energy, depression, muscle mass, memory/concentration, sexual desire, and overall appearance; preventing aging; and losing weight (Table 6).

Source of recommendations and prescriptions. The majority of women using HT (88% of FDA-HT users and 72% of C-HT users) received an HT recommendation from a doctor. C-HT users were more likely to have had HT recommended by a family member, friend, nurse practitioner, and to a lesser degree, by a long list of non-medical sources, including television personalities, media figures, and Internet sites (Table 7). All of the nonmedical sources were selected more frequently by C-HT users than by FDA-HT users.

Gynecologists were most frequently cited to be the prescriber for both FDA-HT (65%) and C-HT (47%). C-HT users more often indicated that the prescriber was "other, not sure" (14%) than FDA-HT users (5%) (Table 8).

Reported benefits. Both C-HT and FDA-HT users reported a wide variety of benefits from their therapies. The most frequently reported benefit by each HT-user group was alleviation of VMS. Only three benefits differed significantly. More FDA-HT users than C-HT users reported alleviation of hot flashes, 40% and 31%, respectively. More FDA-HT users

TABLE 5. *Beliefs regarding safety of "natural" and/or "bioidentical" hormones, expressed as percentages*

Belief	C-HT (n = 326)	FDA-HT (n = 738)
Safer	42	25[a]
Less safe	3	2
No difference	20	23
Not sure	35	51[a]

Both hormone user groups contain current and past users. Percentages may not total 100% because of rounding.
C-HT, compounded hormone therapy; FDA-HT, US Food and Drug Administration-approved hormone therapy.
[a]$P < 0.05$, C-HT vs FDA-HT.

TABLE 6. *Reasons for taking hormone therapy, expressed as percentages*

Reason for HT use	C-HT (n = 326)	FDA-HT (n = 738)
Hot flashes or night sweats	71	70
Vaginal dryness	23	28
Bone health and prevent osteoporosis	21	28[a]
Moodiness or irritability	28	23[a]
Sleep problems	21	13[a]
Discomfort with sexual activity	16	13
Low energy level	17	8[a]
Memory or concentration	13	7[a]
Low sexual desire	14	6[a]
Overall appearance, skin, hair	12	6[a]
Prevent or control aging	13	5[a]
Depression	9	4[a]
Muscle mass	8	4[a]
Lose weight	6	1[a]

Both HT user groups contain current and past users. Participants were asked to check all that apply.
C-HT, compounded hormone therapy; FDA-HT, US Food and Drug Administration-approved hormone therapy; HT, hormone therapy.
[a]*P*-value < 0.05, C-HT vs FDA-HT.

TABLE 7. *Persons or resources recommending participant consider taking hormone therapy, expressed as percentage*

Source of HT recommendation	C-HT (n = 326)	FDA-HT (n = 738)
Doctor	72	88
Family member	12	8
Friend/s	11	7
Nurse or Nurse Practitioner	9	6
Magazine	2	1
Internet ad	2	1
Book	2	0
TV or radio ad	2	0
Antiaging specialist[a]	3	0
TV personality	3	0
Counselor or psychologist	2	0
Other	2	0
No one suggested	10	6
Not sure	1	1

Both HT user groups contain current and past users. Participants were asked to check all that apply.
C-HT, compounded hormone therapy; FDA-HT, US Food and Drug Administration-approved hormone therapy; HT, hormone therapy.
[a]Classifying characteristic.

(9%) also reported benefit for vaginal dryness than did C-HT users (5%). More C-HT users (18%) than FDA-HT users (12%) reported "better mood/more energy." "Other" unspecified benefits were selected more frequently by C-HT users (11%) than by FDA-HT users (7%). All other benefits were reported at a rate of 10% or less, and 16% of both groups reported "none, few benefits." Only 5% selected "overall well-being, quality of life is better" (Table 9).

Reported side effects. Among all HT users, 73% reported they had experienced no side effects. Of the 14% who indicated they had experienced a side effect and the 12% who were not sure, the most common side effects reported were breast tenderness and changes in hair pattern (Table 10). Acne was reported more frequently by the C-HT users than by the FDA-HT users. There was a slightly higher rate of vaginal bleeding among C-HT users than among FDA-HT users, and four reports of endometrial cancer among the 326 C-HT users compared with none among the 738 FDA-HT users.

TABLE 8. *Clinician who prescribes/prescribed hormone therapy, expressed as percentage*

Prescriber	C-HT (n = 326)	FDA-HT (n = 738)
Gynecologist	47	65[a]
Family practice doctor	25	23
Nurse or Nurse Practitioner	5	3[a]
Internist	4	2
Endocrinologist	2	1
Antiaging doctor[b]	2	0
Internet doctor	1	0
Other	9	4[a]
Not sure	5	1[a]

Both hormone user groups contain current and past users. Percentages may not total 100% because of rounding.
C-HT, compounded hormone therapy; FDA-HT, US Food and Drug Administration-approved hormone therapy.
[a]$P < 0.05$, C-HT vs FDA-HT.
[b]Classifying characteristic, statistical analysis not applied.

TABLE 9. *Benefits of hormone therapy, expressed as percentage*

Benefits	C-HT (n = 326)	FDA-HT (n = 738)
Alleviate hot flashes, sweating	31	40[a]
Better mood, more energy	18	12[a]
Alleviates/Delays overall menopausal symptoms	10	7
Better vaginal health (dryness)	5	9[a]
Better sleep	8	6
Better bone health	4	6
Overall well-being, quality of life is better	5	4
Better skin, hair, nails; looked younger	4	4
Better sex life, libido, less pain	5	3
Other benefits	11	7[a]
None or few benefits	16	16
Caused other problems, side effects	2	2
Don't know/Not sure/Can't remember	5	7

Both hormone user groups contain current and past users. Participants were asked to check all that apply.
C-HT, compounded hormone therapy; FDA-HT, US Food and Drug Administration-approved hormone therapy.
[a]$P < 0.05$, C-HT vs FDA-HT.

Duration of use. For both C-HT and FDA-HT users, duration of use ranged from less than 1 year to more than 20 years (Fig. 3). A higher percentage of C-HT users had used HT for less than 3 years, whereas beyond 3 years of use, FDA-HT users had the higher percentage.

When asked how long they expected to continue using HT, 63% of FDA-HT users and 54% of C-HT users indicated that they had already discontinued HT. Of the remaining participants who were still using HT, 15% overall indicated that they were unsure, 8% of both groups selected either they "will not stop" or they will continue to use HT "until I have a problem." Approximately 4% of all hormone users indicated that they planned to use HT for more than 5 more years, whereas the remainder anticipated less than 1 year to 5 years of additional use.

Testosterone use versus other hormone use

Extent of use. Women who were unsure what hormone they were taking were not included in the analyses comparing

TABLE 10. *Frequency of side effects of hormone therapy reported as a percentage of those who indicated they had experienced a side effect or were unsure*

Side effect	C-HT (n = 92)	FDA-HT (n = 191)
Breast tenderness	20	18
Hair pattern changes	18	16
Vaginal bleeding	11	8
More assertive/angry	12	7
Acne	13	6
Problem with gallbladder	6	7
Breast cancer	5	6
Blood clots in legs	5	4
Blood clots in lungs	1	3
Enlarged clitoris	2	1
Cancer of the uterus	4	0
Stroke	1	0
Heart attack	0	0
Other	21	26
No side effect	28	30

Both hormone user groups contain current and past users. Participants were asked to check all that apply.
C-HT, compounded hormone therapy; FDA-HT, US Food and Drug Administration-approved hormone therapy.

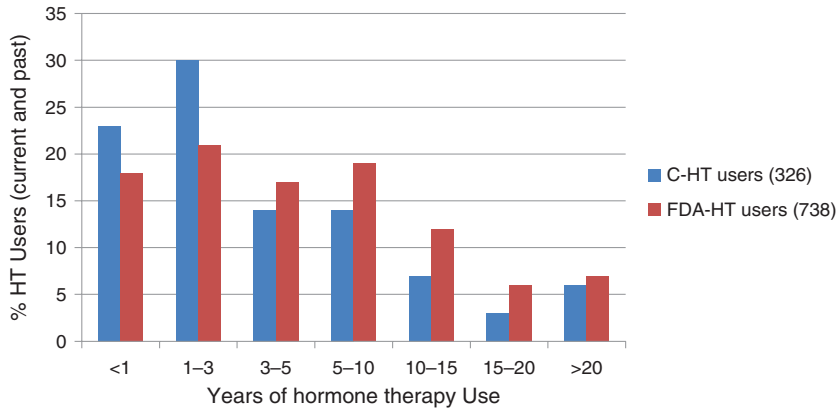

FIG. 3. Duration of hormone therapy use by C-HT users compared with FDA-HT users.
C-HT, compounded hormone therapy; FDA-HT, US Food and Drug Administration-approved hormone therapy; HT, hormone therapy.

testosterone users with other HT users. Testosterone users comprise approximately 13% of all HT users and approximately 4% of the entire survey cohort.

Rates of testosterone use varied across the country. As with HT use, the South had the highest percentage (55%) of the identified testosterone users, whereas the Midwest had the lowest (11%). The West accounted for 18% and the Northeast for 16% of users. Whites/Caucasians comprised 62% of all respondents and the largest share (67%) of testosterone users. Fewer testosterone users had post-high school education than other HT users, 45% versus 58%, respectively. Some of the 136 testosterone users also used other hormones at the following rates: estrogen, 7%; estradiol, 2%; progesterone, 6%; and DHEA, 2%.

Characteristics of testosterone users. Testosterone users had a lower rate of hysterectomy than other HT users, 38% versus 54% ($P < 0.05$), but the percentage of hysterectomies that included removal of both ovaries was similar (Table 11). The person recommending testosterone therapy was less frequently a doctor for testosterone users (72%) than for other HT users (86%) ($P < 0.05$). More testosterone users selected "other/not sure," which suggests prescribing by less-traditional HT providers (Table 11). A lower percentage of testosterone users than other HT users indicated they had received drug risk/benefit information from their provider (64% vs 78%; $P < 0.05$).

The most frequently selected reasons for using testosterone were to treat/improve hot flashes (68%), moodiness/irritability (28%), vaginal dryness and prevention of osteoporosis (20% each), energy level (14%), discomfort with sex (12%), sleep (11%), low desire (10%), and prevent/control aging (9%). Participants could select all that applied.

Benefits that were reported more frequently by testosterone users than by other HT users included better mood/more energy (15% vs 14%) and better sex life/libido/less pain (4% vs 3%), neither of which was statistically significant. The remaining benefits (such as those listed for HT users in Table 9) were reported with the same frequency or higher frequency by the other HT users than by testosterone users, but none achieved statistical significance (data not shown).

A larger percentage of testosterone users (70%) than other HT users (57%) discontinued their hormones within 5 years ($P < 0.05$). The small percentage using testosterone or other HT for more than 20 years was similar in both groups—5% versus 7%, respectively. Testosterone users were slightly more likely to report "none, few benefits" (18%) than other HT users (14%) (Table 11). Overall, testosterone users reported side effects at a rate similar to other HT users (12% vs 15%). Among those reporting side effects, testosterone users had slightly higher percentages than other HT users of "changes in hair pattern" (21% vs 17%) and "more

TABLE 11. *Selected comparisons between testosterone users and all other hormone therapy users reported as percentage of specific user group*

Variable	Testosterone users (n = 136)	All other hormone users (n = 832)
Hysterectomy	38	54[a]
Both ovaries removed with hysterectomy	72	75
Doctor recommended	72	86[a]
Gynecologist prescribed	47	62[a]
Prescriber other/not sure	17	6[a]
Received risk/benefit information	64	78[a]
Reason to use[b]		
Improve energy	14	11
Improve desire	10	9
Prevent/Control aging	9	8
Had benefit[b]		
Hot flashes	31	39
Better mood, more energy	15	14
Libido, sex life	4	3
Other benefits	8	8
Benefits none, few	18	14
Had side effect	12	15
Not sure if had side effect	18	11[a]
Used less than 3 years	60	40[a]

Both hormone user groups contain current and past users.
[a]$P < 0.05$, testosterone users vs all other hormone users.
[b]Participants were asked to check all that apply.

assertive or angry" (13% vs 7%), but the differences were not statistically significant. However, a significantly higher percentage of testosterone users (18%) than other HT users (11%) indicated that they were not sure whether they had experienced a side effect, perhaps reflecting that fewer testosterone users had been given information regarding the potential side effects of testosterone (Table 11).

Selected comparisons between testosterone users and other HT users are included in Table 11. The data on testosterone users are presented as exploratory, because the numbers are small, and few are statistically significant, but they may inform future surveys on this important topic.

DISCUSSION

Conventional HT continues to be the mainstay of treatment for menopausal symptoms despite negative publicity related to its risks, but the market has shifted. As our survey reveals, C-HT users now account for 31% of all HT ever-users aged 40 to 84 years and 34% of current users. Among women aged 40 to 49 years, C-HT users represented 41% of HT ever use. This finding suggests an increasing trend in C-HT use among women entering menopause. The high prevalence of C-HT use detected by our survey is within the range (28% to 68%) that was previously reported.[14] It is of interest to explore why so many women have chosen C-HT over the more than 30 FDA-HT approved formulations that are available in multiple doses with a variety of delivery modes (pill, patch, gel, spray, emulsion, and vaginal creams, tablets, and rings).

The results of this survey suggest several explanations for the increasing use of C-HT. First and perhaps foremost, it appears that many women believe C-HT is "natural" and safer than FDA-HT, a finding corroborated by others.[14,31,32] A recent publication suggested that the word *natural* has a special lure in contemporary culture.[33] Websites of compounding pharmacies often use the words *natural* and *safe,* even though C-HT does not meet the definition of *natural,* and there is no credible evidence that C-HT is safer or more effective than FDA-HT.[34] In addition, some women take C-HT with the expectation of unproven benefits, including improved overall appearance or aging prevention.

Misleading promotion of C-HT by media sources and celebrities without medical expertise may contribute to women's misperceptions. This survey confirmed that C-HT users were more likely to have had HT recommended by a nonmedical source. Our survey also found that current users of C-HT are younger, but past users of FDA-HT are predominantly older women. It is probable that younger women who became aware of potential HT risks published in 2002 sought or were encouraged by their practitioners to take alternative HT that women and/or practitioners believed were safer. Financial incentives for some practitioners might also be a consideration. In addition, many older women were likely to have started FDA-HT on the recommendation of their gynecologists at the time of natural or surgical menopause and took it for a number of years before discontinuing it.

With respect to benefits for the classic indications for HT use, namely VMS, vaginal dryness, and bone health, more women in this survey using FDA-HT reported benefit than did C-HT users. This study is too small to make a definitive statement about side effects, but the higher rates of self-reported bleeding and endometrial cancer in the C-HT group are of significant concern and warrant greater scrutiny. These findings add weight to anecdotal reports already published.[35,36] Topical progesterone often is prescribed by C-HT providers, despite evidence that topical progesterone is not adequate for endometrial protection.[37] Extensive data on outcomes related to HT use are available for FDA-HT and should be collected for women using C-HT.

Strengths of the survey include a US Census-matched cohort and minimal eligibility requirements of sex, age, and menopausal status. Further, the survey provides needed data regarding C-HT use by means of a professionally conducted survey. Our survey provides an estimate of the extensive use of C-HT and provides new information about the use of testosterone by women. Weaknesses of this survey include the relatively small sample size, the low response rate typical of online surveys, the cross-sectional approach, and the difficulty of ascertaining precisely which hormone preparations women were taking. Women commonly take more than one hormone, and in some cases, women may be using a combination of C-HT and FDA-HT. The combination of estrogens, progestogens, and androgens makes it difficult to determine the source of benefits, risks, and side effects. Teasing out more specific information requires longer and more-detailed surveys that are difficult and costly to conduct.

In conclusion, the survey reveals that one in three current users of HT is using C-HT. This finding indicates that the use of non-FDA-approved HT to treat menopausal symptoms is widespread. The need for treatment of menopausal symptoms is being addressed in the United States by extensive promotion, production, and prescribing of C-HT. The amount goes far beyond the sanctioned role of compounding as a resource for patients who are intolerant of a component of FDA-HT.

The widespread use of C-HT suggests a double standard among prescribers who acquiesce to patient demand for C-HT but otherwise prescribe FDA-approved medical therapies for treatment of hypertension, osteoporosis, and other midlife health concerns. The magnitude of C-HT use also reveals a double standard in regulation of the medication supply chain. Pharmaceutical companies are held to FDA-stipulated and enforced standards of manufacturing, requiring demonstrated efficacy, safety, and purity. Meanwhile, the compounding industry currently operates under inconsistent state regulation and oversight and is not uniformly held to FDA standards. High manufacturing standards and assurance of public safety with regard to C-HT will prevail only when national data collection and oversight are federally mandated and complemented by clinical trials of safety and efficacy.

REFERENCES

1. Steinkellner AR, Denison SE, Eldridge SL, Lenzi LL, Chen W, Bowlin SJ. A decade of postmenopausal hormone therapy prescribing in the United States: long-term effects of the Women's Health Initiative. *Menopause* 2012;19:616-621.
2. Tsai SA, Stefanick ML, Stafford RS. Trends in menopausal hormone therapy use of US office-based physicians, 2000-2009. *Menopause* 2011;18:385-392.
3. MacLennan AH, Gill TK, Broadbent JL, Taylor AW. Continuing decline in hormone therapy use: population trends over 17 years. *Climacteric* 2009;12:122-130.
4. Hersh AL, Stefanick ML, Stafford RS. National use of postmenopausal hormone therapy: annual trends and response to recent evidence. *JAMA* 2004;291:47-53.
5. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321-333.
6. Manson JE, Chlebowski RT, Stefanick ML, et al. Menopausal hormone therapy and health outcomes during the intervention and extended post stopping phases of the Women's Health Initiative randomized trials. *JAMA* 2013;310:1353-1368.
7. Merriam-Webster. Definition of bioidentical. Available at: http://www.merriam-webster.com/dictionary/bioidentical. Accessed May 15, 2015.
8. Bhavnani BR, Stanczyk FZ. Misconception and concerns about bioidentical hormones used for custom-compounded hormone therapy. *J Clin Endocrinol Metab* 2012;97:756-759.
9. US Food and Drug Administration. Bio-Identicals: Sorting Myths from Facts. April 8, 2008. FDA Consumer Health Information. Available at: http://www.fda.gov/downloads/ForConsumers/ConsumerUpdates/UCM049312.pdf. Accessed March 8, 2015.
10. Sellers S, Utian WH. Pharmacy compounding primer for physicians. Prescriber beware. *Drugs* 2012;72:2043-2050.
11. State of Tennessee Office of the Attorney General and Reporter. State of Tennessee v HRC Medical Centers. First amended complaint for temporary and permanent injunction, judicial corporate dissolution, and other relief. Case No. 12C4047. Available at: http://attorneygeneral.tn.gov/cases/hrc/hrcamendedcomplaint.pdf. Accessed July 11, 2015.
12. Smith RM, Schaefer MK, Kainer MA, et al. Fungal infections associated with contaminated methylprednisolone injections. *N Engl J Med* 2013;369:1598-1609.
13. FDA takes action against compounded menopause hormone therapy drugs [press release]. January 9, 2008. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116832.htm. Accessed June 18, 2015.
14. Pinkerton JV, Santoro N. Compounded bioidentical hormone therapy: identifying use trends and knowledge gaps among US women. *Menopause* 2015;22:926-936.
15. Mirkin S, Krasssan M, Bernick B, Constantine GD. Usage of FDA-approved and compounded menopausal hormone therapy in the USA following the WHI study. *Menopause* 2014;21:1357.
16. MacLennan AH. Evidence-based review of therapies at the menopause. *Int J Evid Based Healthc* 2009;7:112-123.
17. Yuksel N, Brochu L, Malik B, Bayot A. Promotion and marketing of bioidentical hormone therapy on the internet: a content analysis of websites. *Menopause* 2014;21:1329.
18. Bioidentical Hormone Doctors. Bioidentical Hormones-Oprah Talks. October 9, 2012. Available at: https://www.youtube.com/watch?v=7kEffjzrlLQ. Accessed May 22, 2015.
19. Oprah.com. To: Oprah Winfrey; Subject: Hormones. What I know for sure. Available at: http://www.oprah.com/article/omagazine/200902_omag_oprah_for_sure. Accessed May 22, 2015.
20. Somers S. *Ageless: The Naked Truth About Bioidentical Hormones*. New York: Crown Publishing Group, Random House; 2006.
21. Cobin RH, Petak SM, Bledsoe MB. American Association of Clinical Endocrinologists (AACE) Reproductive Medicine Committee position statement on bioidentical hormones. July 15, 2007. Available at: https://www.aace.com/files/position-statements/aacebhstatement071507.pdf. Accessed June 16, 2015.
22. American College of Obstetricians and Gynecologists Committee on Gynecologic Practice; American Society for Reproductive Medicine Practice Committee. Compounded bioidentical menopausal hormone therapy. *Fertil Steril* 2012;98:308-312.
23. American Medical Association, *FDA Oversight of Bioidentical Hormone (BH) Preparations. Resolution 706* in *AMA House of Delegates Meeting*. 2006: Las Vegas, NV.
24. The Endocrine Society. Position Statement: Bioidentical Hormones. October 2006. Available at: https://www.endocrine.org/advocacy-and-outreach/position-statements. Accessed August 5, 2015.
25. The North American Menopause Society. The 2012 hormone therapy position statement of The North American Menopause Society. *Menopause* 2012;19:257-271.
26. Pinkerton JV. What are the concerns about custom-compounded "bioidentical" hormone therapy? *Menopause* 2014;21:1298-1300.
27. Moyer VA; US Preventive Services Task Force. Menopausal hormone therapy for the primary prevention of chronic conditions: US Preventive Services Task Force recommendation statement. *Ann Intern Med* 2013;158:47-54.
28. McBane SE, Borgelt LM, Barnes KN, Westberg SM, Lodise NM, Stassinos M. Use of compounded bioidentical hormone therapy in menopausal women: an opinion statement of the Women's Health Practice and Research Network of the American College of Clinical Pharmacy. *Pharmacotherapy* 2014;34:410-423.
29. Harlow SD, Gass M, Hall JE, et al. Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. *Menopause* 2012;19:387-395.
30. United States Census Bureau. Annual population estimates: US population by year. Available at: https://www.census.gov/popclock/data_tables.php?component=growth. Accessed July 4, 2015.
31. Iftikhar S, Shuster LT, Johnson RE, Jenkins SM, Wahner-Roedler DL. Use of bioidentical compounded hormones for menopausal concerns: cross-sectional survey in an academic menopause center. *J Women's Health (Larchmt)* 2011;20:559-565.
32. Rosenthal MS. The Wiley Protocol: an analysis of ethical issues. *Menopause* 2008;15:1014-1022.
33. Fishman JR, Flatt MA, Settersten RA Jr. Bioidentical hormones, menopausal women, and the lure of the "natural" in U.S. anti-aging medicine. *Soc Sci Med* 2015;132:79-87.
34. US Food and Drug Administration. Report: limited FDA survey of compounded drug products. June 18, 2009. Available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm155725.htm. Accessed June 18, 2015.
35. Davis R, Batur P, Thacker HL. Risks and effectiveness of compounded bioidentical hormone therapy: a case series. *J Womens Health* 2014;23:642-648.
36. Eden JA, Hacker NF, Fortune M. Three cases of endometrial cancer associated with "bioidentical" hormone replacement therapy. *Med J Aust* 2007;187:244-245.
37. Wren BG, Champion SM, Willetts K, Manga RZ, Eden JA. Transdermal progesterone and its effect on vasomotor symptoms, blood lipid levels, bone metabolic markers, moods, and quality of life for postmenopausal women. *Menopause* 2003;10:13-18.

