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Compounded bioidentical hormone therapy: identifying use trends and knowledge gaps among US women

JoAnn V. Pinkerton, MD,[1] and Nanette Santoro, MD[2]

Abstract

Objective: Two surveys (Harris and Rose surveys) were conducted to quantify the use of compounded hormone therapy (CHT; or bioidentical hormone therapy) among perimenopausal and postmenopausal women in the United States, to assess women's knowledge of CHT versus Food and Drug Administration (FDA)–approved hormone therapy, and to gather information on menopausal experience.

Methods: The Harris survey was administered to 801 women aged 45 to 60 years who had experienced at least one menopausal symptom. The Rose survey was administered to 2,044 women aged 40 years or older who were ever users of hormone therapy. Women were queried about menopausal symptoms, hormone therapy use, and knowledge of CHT. Findings from the Rose survey were extrapolated using US Census Bureau data and prescription claims for FDA-approved hormone therapy to estimate the prevalence of CHT use.

Results: According to extrapolations using Rose data, up to 2.5 million US women aged 40 years or older may use CHT annually, accounting for 28% to 68% of hormone therapy prescriptions. Harris data showed that 86% of women surveyed were unaware that CHT products are not FDA-approved. The Rose survey asked a subset of 1,771 women whether their hormone therapy had been personalized based on hormone levels; 21% (378) answered ''yes'' whereas 27% (476) did not know. In both surveys, most hormone therapy users stated that their physician had recommended the treatment.

Conclusions: We estimate that 1 million to 2.5 million US women aged 40 years or older use CHT. The data suggest that many women are unaware that compounded hormones have not been evaluated or approved by the FDA. Providers have an educational opportunity to ensure that women considering hormone therapy understand the risks and benefits of inadequately regulated CHT.

Key Words: Compounded hormone therapy – Menopause – Bioidentical – Vasomotor symptoms – Hot flashes.

Hormone therapy (HT) effectively treats moderate to severe vasomotor symptoms (VMS) and symptomatic vaginal atrophy and prevents postmenopausal osteoporosis in women transitioning through menopause.[1] Although the use of commercially manufactured HT to treat menopausal symptoms has declined during the past 12 years in response to the now well-known safety findings of the Women's Health Initiative trials (primarily for women aged 60 y or older),[2-8] use of custom compounded hormone therapy (CHT) seems to have increased.[9-12] This seemingly paradoxical increase in CHT use suggests that postmenopausal women do not apply their concerns about the class effects of estrogens and progestogens identified in the Women's Health Initiative to CHT products.

Another driving force behind the use of CHT seems to be the absence of regulation governing product advertising, which allows purveyors of CHT to make unsubstantiated claims about its safety and efficacy.[12,13] In addition, high-profile celebrities such as Oprah Winfrey and Suzanne Somers have promoted CHT to postmenopausal women.[14,15] Physicians and pharmacists who stand to benefit economically from the sales of CHT may also have encouraged its use.[13,16,17]

Although the general consensus is that use of CHT has grown,[9,11,18] prescriptions for CHT are not systematically tracked in the United States, and no one knows exactly how many women are managing their menopausal symptoms with compounded hormones. In a survey of 184 women visiting a physician at the Mayo Clinic Women's Health Clinic (Rochester, MN) about 8 years ago, Iftikhar et al[19]

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From the [1]University of Virginia Health System, Charlottesville, VA; and [2]University of Colorado School of Medicine, Aurora, CO.
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Address correspondence to: JoAnn V. Pinkerton, MD, University of Virginia, Box 801104, Charlottesville, VA 22908. E mail: JVP9U@hscmail.mcc.virginia.edu

found that 14% of respondents were current CHT users; this was twice the rate of prior CHT users. However, because of the survey's age and small nonrepresentative convenience sample, it cannot be assumed that these findings would apply to a broader population of postmenopausal women today.

Recently, two large Internet surveys of middle-aged or older US women were conducted one conducted by Harris Interactive Inc (Harris) and one conducted by Rose Research LLC (Rose) to measure the prevalence of HT and CHT use in the United States and to evaluate the extent to which perimenopausal and postmenopausal women recognize that CHT products are not approved by the US Food and Drug Administration (FDA). From the Rose survey, we extrapolated information on trends in HT use to US Census Bureau figures and used a report on HT prescriptions generated from Symphony Health's Pharmaceutical Audit Suite (PHAST) 2.0 database (Symphony Health, Horsham, PA) of US prescription information to estimate the amount of CHT used in the United States and the proportion of HT prescriptions that are compounded. We also examined survey data on menopausal experience, knowledge of and practices regarding HT, and treatment outcomes. We anticipated that the data would show a high rate of CHT use and limited knowledge regarding the regulatory status of CHT in a sample of reasonably representative perimenopausal and postmenopausal women.

METHODS

Survey design

The market research firms Harris and Rose each administered a population-based, cross-sectional Internet survey on menopause and HT to US women. The source populations were drawn from Web-based nonprobability consumer panels maintained by Harris and Global Market Insite (GMI). Members were recruited to their respective panels primarily through Internet recruitment drives (eg, advertisements and newsletters) and opted to join the panels. Privacy policies were fully disclosed to each member at registration, at which time they submitted a profile containing their E-mail address, name, home address, age, and other demographic information. An e-mail was sent to the e-mail address recorded at registration, with a link for panel applicants to confirm their desire to join the panel and to sign a confidentiality agreement.

The Harris survey was conducted between June 24 and July 10, 2013, and the Rose survey was conducted during three consecutive weeks in April 2014. The sample population was invited via e-mail to take the survey during the defined time frame. The e-mail provided an encrypted link to the survey, which is housed on a secure database and must be completed in a single sitting. Participation was voluntary, no medical procedures were conducted, and risk to participants was considered minimal. Although a written informed consent form was not formally obtained, respondents were advised before they began the survey that their opinions regarding medications or products that they might be taking for health were being sought, and they were assured that their answers and identifying information would remain confidential.

Responses were captured electronically and stored on a secure private server. Survey administrators applied several techniques to exclude duplicate or fraudulent responses. Respondents' digital fingerprints were compared with their registered profile, and surveys completed in less than two fifths of the median time estimated for completion were excluded. Only aggregated deidentified data were provided for analyses. As a reward for completing the survey, panel members received sweepstakes entries and/or points redeemable for approximately US$10 in cash or merchandise.

Harris and GMI are members of The World Association for Opinion and Marketing Research and comply with the International Chamber of Commerce/World Association for Opinion and Marketing Research International Code on Market and Social Research. Harris also conforms to the American Association for Public Opinion Research Code of Professional Ethics and Practices, the Health Insurance Portability and Accountability Act, and other US privacy regulations and guidelines.

Sample and inclusion criteria

For the Harris poll, women aged 45 to 60 years who were currently going through menopause or had experienced menopause were eligible to participate. With the goal of accruing 800 completed surveys, Harris invited 10,781 women aged 45 to 60 years from its consumer panel to take a survey on an unspecified topic. Invitations were balanced by US Census Bureau statistics for age, race, geographic location, household income, and education levels; invitees were systematically sampled from among panel members matching each target demographic. Quotas were established according to the desired number of completers per demographic attribute, and additional invitations were sent in batches in blinded fashion until each quota was met. These steps were taken to help mitigate sample biases and to ensure reliable and projectable survey results.

For the Rose survey, women aged 40 years or older who (1) confirmed current or former use of an HT product from a list of generic and branded drugs approved by the FDA to treat menopausal symptoms or (2) identified themselves as ever users of any product for ''hormone therapy replacement or supplement'' were eligible to participate. Women who did not indicate current or prior use of an HT product on the list or who answered ''no'' when asked whether they had ever used any product for ''hormone therapy replacement or supplement'' were excluded. In all, 90,120 women aged 40 years or older who belonged to the GMI consumer panel were invited, with the intent of obtaining 2,000 completed surveys. As with the Harris poll, the Rose survey used systematic sampling of panel members to ensure that the number of women invited per demographic attribute comported with US Census Bureau figures. Additional responses were sent in waves until response quotas for all demographic categories were satisfied.

Throughout this report, women who responded to the invitation are referred to as ''respondents.'' Those respondents who were deemed eligible after answering all screening

questions and who completed the remainder of the survey are referred to as ''completers.''

Survey instrument

Questionnaires were developed by TherapeuticsMD in conjunction with survey administrators. Before the Rose survey was fielded, it was tested for face validity among a sample of 100 women and adjusted as needed. Each of the finalized surveys took about 15 minutes to complete. Most questions were multiple choice and allowed participants to select only one answer. Answer choices were rotated randomly for each participant to minimize potential bias, and a response was required before proceeding to the next question.

Harris respondents were asked whether they had ever experienced menopausal symptoms and whether they were currently experiencing them. Both Harris and Rose completers were asked about age at menopausal symptom onset, whether they had ever experienced specific menopausal symptoms, and severity of any symptoms. Completers in both surveys were also asked about HT use (type, where obtained, duration, and effectiveness) and specifically about CHT use. Because CHT is described in different ways, pertinent questions attempted to define CHT using terminology associated with how this treatment is prescribed. Harris completers were given a list of treatments of menopause symptoms and asked to indicate any treatment they had tried, including ''bioidentical hormone replacement therapy (HRT) from a specialty pharmacy (personalized specifically for you by a special compounding pharmacy local or mail order/Internet).'' Ever users in the Rose survey were asked, ''Was your prescription for hormone therapy specifically formulated, personalized, or compounded specifically for you based on your hormone levels?'' This question was added to the survey after 273 of the eventual completers had already taken the survey to permit the collection of more complete information on CHT use. Only Harris completers were asked, ''Do you believe that bioidentical hormone therapies compounded at a specialty pharmacy are FDA-approved?''

Data analyses

Weighting by US Census Bureau statistics was applied to the final pool of Harris respondents to ensure that demographic attributes of age, race, and geographic distribution were proportional with the general population of US women. The Harris survey also weighted results to the US population by age, income level, educational status, and race, which did not materially affect outcomes. The pool of Rose respondents yielded a population of completers well-matched to the general population on target demographic variables and did not require weighting. Both surveys were slightly underweighted for race (80%-84% of completers were white). In analyzing data for eligible completers, we considered only women who answered 100% of the survey questions posed; partial interviews were excluded.

For the Rose survey, responses were analyzed for the entire pool of completers and stratified by age (40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, and ≥80 y). Subset analyses were conducted for women aged 50 to 64 years, which is the age group more likely to experience menopausal symptoms. In addition, responses were stratified by region, income level, ethnicity, current or former use, and hysterectomy or menopause status (perimenopausal and postmenopausal vs premenopausal).

There is no consensus for calculating response rates or estimating sampling error for a sample drawn from a nonprobability panel.[20] As recommended by the American Association for Public Opinion Research[20] in accordance with terms defined in the International Organization for Standardization report ISO 26362:2009, we reported the participation rate and cooperation rate, calculated as follows:

$$\text{Participation rete} = \frac{\text{Respondents with usable response}}{\text{Invitations sent}}$$

$$\text{Cooperative rate} \quad \frac{\text{Complete interviews}}{(\text{Complete} + \text{partial interviews}) + \text{refusal/breakof}f + \text{other}}$$

We also calculated the qualification rate using the following formula:

$$\text{Qualification rate} \quad \frac{\text{Eligible respondents}}{\text{Respondents with a usable response}}$$

To estimate US trends in CHT use and annual spending on CHT, we used Rose survey information on rate of current HT use, number and cost of HT products used, and duration of use; the 2012 census estimates; and a summary report of HT prescriptions filled by US women aged 18 years or older. The report was generated using PHAST 2.0 (Symphony Health), a database of prescription information collected weekly from retail, mail order, and specialty pharmacies across the United States. (Calculations are detailed in ''Results.'')

RESULTS

Response rates and demographic information

The Harris survey invited 10,781 women aged 45 to 60 years, via e-mail, to participate in an online survey between June 24 and July 10, 2013 (Fig. 1). A total of 1,099 women responded (participation rate, 10%). Of these women, 855 had experienced or were experiencing menopausal symptoms and were thus eligible (qualification rate, 78%). The cooperation rate was 94%, with 801 of 855 eligible women completing the survey.

An invitation to take the Rose survey was e-mailed to 90,210 individuals during a 3-week period in April 2014, and 17,897 invitees responded (participation rate, 20%). Seventy-two respondents were men and were excluded. Screening of the remaining 17,825 Rose respondents identified 2,369 women aged 40 years or older who were currently using or had previously used HT and were eligible to complete the survey (qualification rate, 13%). The cooperation rate was 86%, with 2,044 of 2,369 eligible women completing the survey. Subset analysis in the Rose survey included 855 respondents aged 50 to 64 years, of whom 839 completed

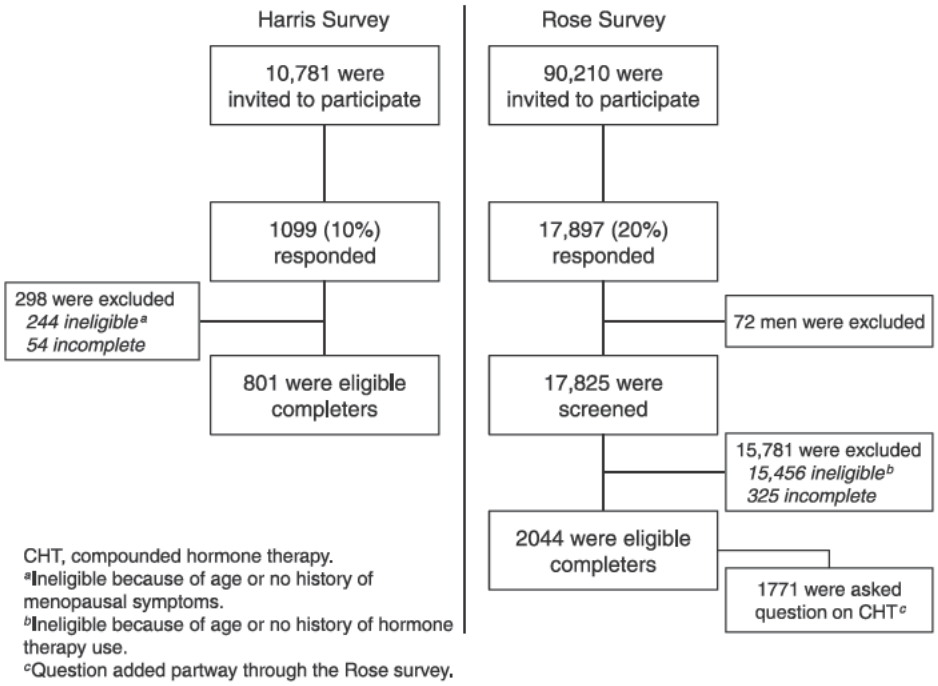

FIG. 1. Survey sample and disposition for the Harris and Rose surveys.

the survey and 714 were asked about CHT use. The cooperation rates among eligible women were very high (94% for the Harris survey and 86% for the Rose survey), with the number of dropoffs in each survey too low to draw meaningful conclusions about differences between eligible completers and noncompleters.

Most completers in the Harris and Rose surveys were white, had some postsecondary education or vocational training, and had public or private healthcare coverage (Table 1). Approximately three quarters of completers in each survey were postmenopausal, having indicated that their last menstrual cycle occurred more than 12 months earlier. We considered the remaining Harris completers perimenopausal because all had experienced menopausal symptoms. In the Rose survey, 5% of completers stated that they had just started menopause, and 7% stated that they had been going through menopause for less than 1 year; these women were considered perimenopausal. Another 15% stated that they had yet to go through menopause and were categorized as nonmenopausal. Among Rose completers aged 50 to 64 years, 84% were postmenopausal, 13% were perimenopausal, and 4% had yet to go through menopause.

Prevalence, cost, and knowledge of CHT

We used a four-step process to estimate the prevalence of CHT use among US women. In step 1, we calculated the estimated number of US women aged 40 years or older who are currently using menopausal HT (compounded and FDA-approved). First, we determined the rate of current HT use for Rose respondents per age range: 40 to 44, 45 to 49, 50 to 54, 55 to 59, 60 to 69, 70 to 74, 75 to 79, and 80 years or older. Next, we multiplied the current use rate for each age range by the total number of same-age US women per US Census Bureau population estimates for 2012 (Table 2).[21] This shows that approximately 3.7 million US women aged 40 years or older currently use HT.

In step 2, we calculated the number of HT prescriptions (compounded and FDA-approved) dispensed annually. We multiplied the estimated 3.7 million current HT users by the mean number of HT products taken per month in the Rose survey (1.7) by the estimated duration of use, which we assumed to range from 9 to 12 months. This suggests that 57 million to 75 million prescriptions for HT are filled annually (Fig. 2).

In step 3, we estimated the number of CHT prescriptions dispensed annually. According to PHAST 2.0 prescription data, approximately 36 million prescriptions for FDA-approved HT were filled in 2012; a small percentage may have been filled for men and for women younger than 40 years (<1%).[6] Subtracting the 36 million annual prescriptions of FDA-approved HT from the 57 million to 75 million annual prescriptions for all HT indicates that 21 million to 39 million prescriptions for CHT may be filled annually, accounting for 28% to 68% of HT use.

In step 4, we determined the number of US women aged 40 years or older using CHT annually by dividing the number of CHT prescriptions filled annually by the mean 1.7 HT products taken per month in the Rose survey (1.7) by assumed duration of use (9-12 mo). This suggests that 1 million to 2.5 million women may use CHT annually.

To calculate the estimated amount spent on CHT annually, we multiplied the number of CHT prescriptions filled annually by the average price of US$49 that Rose completers reported paying out of pocket for HT. Results show that

TABLE 1. *Demographic characteristics of Harris (N = 801; 73%) and Rose (N = 2,044; 11%) completers*

Characteristics	Harris survey	Rose survey
Age group (Harris/Rose)		
40 44 y	NA	278 (14)
45 50/45 49 y	208 (26)	286 (14)
51 55/50 54 y	312 (39)	307 (15)
56-59/55-59 y	280 (35)	287 (14)
60-64 y	NA	245 (12)
65-69 y	NA	186 (9)
70-74 y	NA	145 (7)
75-79 y	NA	125 (6)
≥80 y	NA	185 (9)
Race/ethnicity		
White	641 (80)	1,726 (84)
Black	72 (9)	136 (7)
Hispanic	72 (9)	99 (5)
Other[a]	16 (2)	83 (4)
Highest level of education		
Less than or some high school	NA	46 (2)
Completed high school	264 (33)	372 (18)
Vocational training	NA	94 (5)
Some college (no degree)	NA	485 (24)
Associate's degree	NA	282 (14)
Bachelor's degree	449 (56)	434 (21)
Some graduate school	NA	99 (5)
Graduate degree	88 (11)	232 (11)
Household income for 2012		
US$<25,000	128 (16)	305 (15)
US$25,000-49,999	168 (21)	599 (29)
US$50,000-74,999	144 (18)	434 (21)
US$75,000-99,000	120 (15)	244 (12)
≥US$100,000	216 (27)	335 (16)
Declined to answer	NA	127 (6)
Healthcare coverage		
PPO/HMO	489 (61)	792 (39)
Traditional insurance	56 (7)	239 (12)
Medicare/Medicaid	88 (11)	752 (37)
Other/unknown	56 (7)	165 (8)
No coverage	104 (13)	96 (5)
Prior hysterectomy	160 (20)	927 (45)
Menopause status		
Menopausal[b]	601 (75)	1,594 (78)
Perimenopausal	200 (25)[c]	259 (12)[d]
Nonmenopausal	NA	301 (15)

Data are presented as n (%).
NA, not available; PPO, preferred provider organization; HMO, health maintenance organization.
[a]For the Harris survey, ''other'' includes Asian American and other. For the Rose survey, ''other'' includes Asian American, Pacific Islander, Native American/Alaskan Native, mixed race, and other.
[b]''Menopausal'' refers to women who reported that their last menstrual cycle was more than 1 year ago.
[c]Because eligibility for the Harris survey required at least one menopausal symptom, women who stated that they had not ceased menstruating for 1 year or longer were assumed to be perimenopausal.
[d]In the Rose survey, ''perimenopausal'' refers to women who stated that they had been going through menopause for less than 1 year and included some women who stated that they had stopped menstruating more than 1 year ago.

between US$1 billion and US$2 billion may be spent on CHT each year in the United States.

Reported prevalence of CHT use

Two percent (16 of 801) of Harris completers affirmed that they had used CHT. Assuming that the 16 CHT users belong to the subset of HT ever users (n = 123), CHT use would account for 13% of the total HT used by Harris completers. Twenty-one percent (378 of 1,771) of Rose completers reported current or prior use of personalized CHT, with no difference in the rate of CHT use observed among the subset of women aged 50 to 64 years (153 of 714). Rates of CHT use were higher in the younger age groups and lower in the older age groups compared with the overall population of Rose completers (Fig. 3). Rose completers taking CHT were more than twice as likely as women using conventional HT to obtain it through their physician's office (15% vs 6%, respectively), although women in both groups were most likely to obtain their HT products from a local pharmacy (59% vs 54%, respectively; Fig. 4).

TABLE 2. *Current rate of HT use among Rose respondents extrapolated to an age matched population of US women*

Age range (y)	Number of US women[21]	Current HT use among Rose respondents, by age (%)	Estimated number of US women using HT
40-44	10,569,227	7	739,846
45-49	10,962,854	7	767,400
50-54	11,499,014	5	574,951
55-59	10,704,108	3	321,123
60-64	9,279,200	5	463,960
65-69	7,370,497	3	221,115
70-74	5,412,023	3	162,361
75-79	4,198,131	3	125,944
≥80	7,349,650	5	367,483
Total	77,344,704		3,744,183

HT, hormone therapy.

Knowledge of CHT

All Harris completers (N = 801) were asked, ''Do you believe that bioidentical hormone therapies compounded at a specialty pharmacy are FDA-approved?'' Only 14% correctly answered ''no,'' whereas 10% answered ''yes'' and 76% stated that they were not sure (Fig. 5). When Rose completers (N = 2,044) were asked whether their HT had been personalized or compounded for them, 27% of the women stated that they did not know.

General findings on menopause symptoms and treatment

Any HT use

In the Harris survey, 15% of completers were ever users of HT, 6% were current users of HT, and 9% were prior users of HT. Patterns of HT use among Rose respondents (n = 17,825) were similar, with 13% reporting ever use of HT. Approximately 5% of Rose respondents were current HT users, suggesting that 8% were prior users. In the subset of Rose respondents aged 50 to 64 years, 4% were current users and 6% were prior users. The mean duration of HT use among ever users in the Harris survey was 50 months (Fig. 6A). The Rose survey expressed duration of use as a range. Based on the midpoint for each range, the approximate median use for Rose completers was 28 months (Fig. 6B).

Both surveys showed that HT was generally effective in relieving menopausal symptoms. Approximately 89% of ever users in the Harris survey stated that HT provided moderate or significant relief; 83% of ever users in the Rose survey stated

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