University of Alberta

Pharmacists' Beliefs about Bioidentical Hormone Therapy

by

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ABSTRACT

OBJECTIVE: To identify pharmacists' beliefs about bioidentical hormone therapy (BHT) and determine factors influencing these beliefs**.**

METHODS: This was a cross-sectional survey targeting practicing pharmacists in Alberta. Participants completed a 54-item, online questionnaire, designed to capture their demographics, as well as their beliefs about BHT. Summary statistics and multivariate regression were used for analyses. Qualitative components were analyzed using phenomenological approach.

RESULTS: Over half of respondents believed BHT had equal efficacy and risks as non-bioidentical hormones. Beliefs on estriol, natural progesterone, and saliva testing however, were more diverse with many do not know responses (40%). In multivariate analysis, BHT compounding practice was associated with beliefs about BHT. Qualitative analysis identified contrasting themes between pharmacists who practiced in a BHT compounding pharmacy versus those who did not.

CONCLUSION: Results from this survey indicated that pharmacists had varying beliefs on BHT. This study helps identify areas for targeted education.

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LIST OF ABBREVIATIONS

STRAW	Stages of reproductive aging workshop
FSH	Follicle stimulating hormone
NAMS	The North American Menopause Society
DHEA	Dehydroepiandrosterone
HT	Hormone therapy
SOGC	The Society of Obstetricians and Gynecologists of Canada
CEE	Conjugated equine estrogen
MPA	Medroxyprogesterone acetate
WHI	Women's Health Initiative
EPT	Estrogen-progestin therapy
ET	Estrogen-only therapy
BHT	Bioidentical hormone therapy
Bi-est	Biestrogen
Tri-est	Triestrogen
FDA	US Food and Drug Administration
ACOG	The American Congress of Obstetricians and Gynecologists
RCT	Randomized controlled trial
ACP	Alberta College of Pharmacists
AICT	Academic information and communication technologies
CVD	Cardiovascular disease
VTE	Venous thromboembolism
VIF	Variance inflation factor
KEEPS	Kronos Early Estrogen Prevention Study
ELITE	Early versus Late Intervention Trial with Estradiol
PCCA	Professional Compounding Centers of America
CE	Continuing pharmacy education
SIGMA	The Canadian Menopause Society

CHAPTER ONE

INTRODUCTION

1.1 Menopause

Menopause is a natural part of the female aging process. Most women experience menopause between the ages of 42 and 58 years (1), with the average age of menopause at 51 (2). As women approach menopause they experience a constellation of symptoms that can significantly affect their quality of life. These symptoms include vasomotor, urogenital, sleep disturbances, mood changes, and cognitive symptoms. Among these symptoms, vasomotor (e.g. hot flushes and night sweats) and urogenital (e.g. vaginal dryness, itching, burning and dyspareunia) are the most common. Women may experience menopausal symptoms before the onset of menopause, during the menopause transition. In 2001 a model developed by the Stages of Reproductive Aging Workshop (STRAW) described seven stages of reproductive aging for women, which were sub-classified into: 1) reproductive stages including regular menstrual periods and normal follicle stimulating hormone (FSH) levels; 2) menopausal transition characterized by variable menstrual cycle and high FSH levels; and 3) post-menopause stage starting with final menstrual period and lasting till demise (3). Based on the STRAW classification, the menopause transition begins with variations in the menstrual cycle length and ends at the time of the final menstrual period. The North American Menopause Society (NAMS) often uses the term perimenopause to refer to the menopause transition. Vasomotor symptoms are

often more common during menopause transition, with hot flashes experienced by up to 80% of women during this time (4) (5). On the contrary, urogenital symptoms are more prevalent among post-menopausal women (6, 7).

1.2 Long-term health risks after menopause

The risks of cardiovascular diseases and osteoporosis increase significantly after menopause (7-9). In women, most cardiovascular events occur in the postmenopausal age range (10). Menopause is accompanied by an accumulation of abdominal fat which increases the risk of insulin resistance, hyperlipidemia and hypertension thus cardiovascular disease (11). Furthermore, there is evidence of the beneficial effects of endogenous estrogen on endothelial functions (12), lipids (13), and insulin sensitivity (14). Abdominal obesity, abnormal lipids, and diabetes have been associated with an increased risk for cardiovascular disease in women (15).

Estrogen insufficiency increases the risk of osteoporotic fractures in postmenopausal women (16). The menopause-related reduction in bone mineral density is most evident during the first year after menopause (e.g. 8.1% per year) (17). The rate of bone loss continues progressively according to a logarithmic function, usually settling at a rate of 1-2% per year with great inter-individual variability (17, 18).

1.3 Management of menopause

Lifestyle changes and prescription medications are effective means for maintaining or improving a women's quality of life during menopause. Besides effectively reducing mild menopausal symptoms for symptomatic women, lifestyle interventions can modify risk factors for conditions such as cardiovascular disease and osteoporosis, which are more prevalent among post-menopausal women. These interventions include a balanced healthy diet, moderate exercise, maintenance of healthy body weight, avoidance of smoking, limited alcohol consumption, treatment of underlying disorders (e.g. hypertension, hypercholesterolemia, diabetes), and adequate intake of calcium and vitamin D (9). Health care providers can advise, support and motivate menopausal women to implement these lifestyle changes to optimize their health. Nevertheless, moderate to severe menopausal symptoms may warrant the use of prescription therapies including hormone therapy (HT) and non-hormonal prescription medications. Non-hormonal therapies such as antidepressant agents, gabapentin, clonidine and bellargel are considered when HT is contraindicated or not desired (9). HT is relatively contraindicated in certain clinical situations such as a history of breast cancer, a history of endometrial cancer, severe active liver disease, thromboembolic disorders, and undiagnosed vaginal bleeding (19).

Soy products, red clover, phytoestrogens, black cohosh, dehydroepiandrosterone (DHEA), and others are examples of natural health products for managing menopause. However, limited evidence is available on the

efficacy and safety of these products, therefore they should be used with caution (20).

1.4 Hormone Therapy

1.4.1 Role of hormone therapy

Hormone therapy (HT) has been used for over 60 years to manage menopausal symptoms (21). HT has also been shown to have positive health effects on bones (22). According to current guidelines by the Society of Obstetricians and Gynaecologists of Canada (SOGC) and NAMS, HT is the most effective therapy to relieve menopausal symptoms, and a reasonable choice to prevent osteoporotic fracture and bone loss (23, 24). Moreover, in women with menopausal symptoms who require treatment for osteoporosis, recent guidelines by Osteoporosis Canada also recommend HT as a first line therapy to prevent osteoporotic fractures (25). Systemic estrogen therapy, with or without progestogen, is the mainstay treatment option for vasomotor symptoms (24). Similarly, vaginal estrogen is the most effective treatment for moderate to severe vaginal symptoms (2).

1.4.2 Hormones used in HT

1.4.2.1 Estrogens

HT products contain different types of estrogens. Some of these estrogens are chemically identical to hormones secreted by women, which include estradiol, estrone and estriol. Of these, estradiol is the most potent and is produced by the ovaries. Estrone is reversibly metabolized from estradiol in the liver. Both estrone

and estradiol are metabolized to estriol, the least potent estrogen (26). Estriol has 1/80 the potency of estradiol (27). Several forms of estradiol and estrone (e.g. 17β-estradiol and conjugated estrone sulphate) are available as Health Canada-approved HT products. There is no Health Canada approved product for estriol; however, it is used extensively in compounded preparations (28). These estrogens are mainly synthesized from plant substances extracted from soy and yams (29). Other types of estrogen such as conjugated equine estrogens (CEE) are not structurally similar to human hormones and come from animal sources. CEE's are commercially available in various Health Canada approved HT products.

1.4.2.2 Progestogens

Progestogens include progesterone and synthetic progestins such as medroxyprogesterone acetate (MPA) and norethindrone. Progesterone is the only progestogen naturally secreted in a women's body. In Canada, progesterone synthesized from plant extracts is commercially available as an oral micronized formulation called Prometrium™. Progesterone can also be compounded into various formulations, including transdermal creams by compounding pharmacies.

1.4.3 Shift in HT use

Despite the established benefits of HT, few women who might benefit from HT choose to take it (30). Among those women who start HT, only 40% will remain on it after one year (31). Several factors may play a part in women avoiding HT or discontinuing it early: a global trend toward using " natural products"; the worry over troublesome side-effects of HT; and, most commonly, fear of long-term health risks (e.g. breast cancer) (31). In the late 1990's, media

reports about HT research raised concerns about the therapy's long-term health risks, causing many women to alter their approach toward using HT (32, 33). However not until the publication of the Women's Health Initiative (WHI), was the shift away from HT use most evident.

The WHI, launched in the early 90's, was a set of clinical trials and an observational study planned by the US National Institutes of Health to address the most common causes of impaired quality of life, disability and death in postmenopausal women (34). The observational study was intended to identify predictors of diseases prevalent among postmenopausal women, whereas the randomized clinical trials were designed to identify the effects of HT, diet modification, and calcium and vitamin D supplements on heart disease, fractures, and breast and colorectal cancer. Overall, the study involved more than 161,000 healthy postmenopausal women. The HT clinical trials consisted of two arms: estrogen (CEE) + progestin (MPA) therapy (EPT), and estrogen (CEE)-only therapy (ET). In the EPT arm, more than 16,000 healthy, postmenopausal women between 50 and 79 years were randomly assigned to either the CEE + MPA group or the placebo group. In 2002, after an average of 5.2 years, the study was prematurely halted due to increased risk of invasive breast cancer, myocardial infarction, stroke, and blood clots in the treated group vs. the placebo group. Yet a decrease in the risk of colorectal cancer and hip fractures was observed (35). Investigators concluded that the risks of conventional HT (e.g. CEE and MPA) outweighed the benefits provided (35-37). A year and a half later, in 2004, the ET arm, involving more than 10,000 postmenopausal women who had undergone

hysterectomies and were randomly assigned to the CEE or placebo group, was terminated. The termination occurred one year before the planned conclusion because of an increased risk in stroke and blood clots. Nonetheless, ET had neutral effects on the incidence of heart disease and breast cancer. Similar to EPT's benefits, ET was shown to reduce the risk of colorectal cancer and hip fractures (37).

Shortly after the publication of the EPT study in July 2002, there was a drastic decline in the number of women using HT (23, 38, 39). Relative to the months before July 2002, between July 2002 and July 2003, a 40% decrease in all HT prescriptions was reported in the US (39). In Canada, the number of HT users decreased at an average rate of 17% per year between 2001-2002 and 2006-2007 (23). After the WHI, the media aggressively exploited safety concerns with the use of conventional HT, leading even more health care professionals and women to turn away from conventional HT toward perceived safer alternatives. Recently, there has been much media attention to the use of Bioidentical Hormone Therapy (BHT) as safer alternatives to HT (i.e. Oprah, Susan Summers, etc) (40-42).

1.5 Bioidentical Hormone Therapy

A recently published systematic review by Whelan et al identified 63 different definitions for bioidentical hormones (33). They proposed the following definition to reflect the similarities among the existing definitions: *"chemical substances that are identical in molecular structure to human hormones"* (43). This would include any HT product containing estradiol, estrone, estriol, progesterone, and testosterone. This definition does not address manufacturing

sources and dosage forms, thus includes both Health Canada approved HT products, in addition to non-regulated customized compounded preparations made at compounding pharmacies commonly known as compounded BHT (44, 45).

1.5.1 Confusion with the term

The lack of a consistent definition of bioidentical hormones has led to much confusion. One of the misperceptions is that BHT is only available as compounded HT products specifically made for each patient (46, 47). Nonetheless, many commercially available products containing estradiol, estrone and progesterone would fit the definition of bioidentical hormones. In fact, the raw ingredients used to manufacture BHT, whether federally approved or compounded, are the same (45). Another source of confusion is that BHT is promoted as being made from natural hormones (48). However, using the term "natural" to describe bio-identical hormones is misleading because these products are derived from plant extracts that have undergone synthetic processing to obtain hormones structurally identical to human hormones (49). Thus, no bioidentical hormone is considered 100% natural (50). The term "natural hormones" is usually used to refer to substances that are extracted unchanged from plants or animals (51), such as phytoestrogens, which are extracted from soy products such as soy milk and tofu (52); or CEE's, which come from the urine of pregnant mares. Natural hormones may not always be bioidentical (52).

1.5.2 Compounded BHT

Compounded BHT are formulated using an individualized prescription from a physician. These formulations can be compounded for a variety of administration routes. However, the most common include topical or oral estriol containing formulations, and compounded progesterone cream (53). Examples of compounded estriol formulations include Bi-est (biestrogen), containing estriol and estradiol in a ratio of 8:2 or 5:5; and Tri-est (trestrogen) with estriol, estradiol and estrone in a ratio of 8:1:1 (28, 54). Compounded BHT proponents claim that these ratios were formulated to replicate estrogen levels in the body (26) and can be modified based on symptoms (55). The quality of these products may vary from one compounding pharmacy to the other depending on the compounding technique and bases used in the formulations (56).

Compounded BHT may provide women with therapeutic options in addition to what is commercially available in terms of dosing flexibility, hormone combinations, and alternative routes of administration. However, in contrast to commercially available HT, these products lack well controlled studies examining efficacy, safety, route of administration, pharmacokinetics, and a clear scientific rationale for the mixture and ratios of bioidentical estrogen in preparations (57). Despite the provincial regulation of the act of compounding (58), the absence of federal jurisdiction on compounded BHT may affect these products' quality, purity, dose accuracy, potency, and safety (24, 59, 60).

1.5.3 Controversy over BHT

Advocates promote BHT as being safer and more effective than conventional HT. BHT proponents claim that because these products are an identical match for endogenous hormones, they will have a better fit to human receptors and produce natural biological results with fewer side-effects (61). Furthermore, advocates state that findings from WHI cannot be extrapolated to other HT combinations and that BHT is expected to have a different, safer risk profile (62). There are also claims that are specific to compounded BHT. Among these claims are that an individualized approach offers improved safety, efficacy and tolerability as opposed to the "one-size fits all" approach seen in commercial BHT; the safety of estriol containing formulations over commercially available estrogen preparations; the efficacy of transdermal progesterone cream in endometrial protection for women using systemic estrogen; and the use of saliva testing for hormonal assessment and BHT dose titration (55, 63, 64). These claims are highly adopted by compounding pharmacies. No conclusive scientific data is available to validate or refute any of these assertions.

Evidence that BHT is associated with better outcomes and fewer risks compared to conventional HT is lacking (21, 22, 57, 62, 65-67). Various organizations such as the US Food and Drug Administration (FDA), NAMS, American Congress of Obstetricians and Gynaecologists (ACOG), and the Endocrine Society have reported that there is no scientific evidence that BHT is safer or more effective than other HT (24, 59, 60, 68, 69). These organizations have expressed concern that due to highly publicized claims about BHT, patients

may be receiving potentially misleading or false information about the benefits and risks of BHT. At this time, the benefits and risks are assumed to be the same as those for conventional HT (24, 59, 70).

1.6 Efficacy of BHT

1.6.1 BHT and menopausal symptoms

Estradiol has been well established for improving vasomotor and urogenital symptoms. Vaginal estriol has been shown to improve climacteric symptoms (71-75). However, data on the benefits of oral estriol in relieving menopausal symptoms have been mixed (76-79). Data to support the greater efficacy of estriol over other estrogen is lacking.

Oral micronized progesterone can be used in the treatment of vasomotor symptoms (80). However, the efficacy of transdermal progesterone cream to relieve vasomotor symptoms, is contradictory. In one small-scaled, randomized controlled trial in 102 healthy postmenopausal women, transdermal progesterone cream was shown to significantly improve vasomotor symptoms compared to placebo (81). Nevertheless, two double-blind randomized placebo controlled trials assessing the effect of transdermal progesterone cream in vasomotor symptoms reported that the cream is no more effective than a placebo (82, 83).

1.6.2 BHT and prevention of osteoporotic fractures

CEE's long-term benefits on decreasing the risk of bone loss has also been shown with estradiol (84-86). Most Health Canada approved HT products are indicated for the prevention of osteoporosis (9). Findings on estriol's effects on bone mineral density (BMD) have been inconsistent (76, 78, 87), with the most promising results coming from Japan (88-91). No evidence supports using progesterone cream alone to prevent bone loss (26, 82, 92, 93).

1.7 Risks of BHT

1.7.1 BHT and cardiovascular risks

An increased incidence of adverse cardiovascular events among EPT users has been shown in randomized clinical trials (35, 94). BHT proponents attribute these findings to the non-bioidentical and synthetic nature of hormones used in these trials (CEE and MPA respectively). This belief was supported by smaller studies suggesting that oral CEE contributes to a greater increase in triglycerides compared to bioidentical estrogens (88, 95). Similarly, other studies suggest the benefits of progesterone over synthetic progestins on the arteries and lipid profile (96, 97). However, data from these studies are only hypothesis generating. Until large-scale, randomized, controlled, clinical trials (RCT's) similar in scope to the WHI compare BHT to placebos, it's too early to draw any conclusions.

1.7.2 BHT and endometrial cancer

The proliferative effects of estrogens on the endometrial lining are well-known. Combining estrogen therapy with progestogen has been shown to reduce the risk of endometrial hyperplasia (98). Clinical practice guidelines recommend that every woman with an intact uterus who chooses to use systemic HT should be advised to use combined estrogen/progestogen therapy (2, 24). Similar to other estrogens, oral estriol has been shown to induce endometrial hyperplasia (99-102) and increase the risk of endometrial cancer (98). Data supporting the safety of estriol containing topical cream (e.g.bi-est and tri-est) on the endometrium is lacking. Estriol should not be used without progesterone in women with an intact uterus (26).

It is unclear if progesterone cream in combination with estrogens provides enough protection against endometrial hyperplasia. Few studies, which involved only a small number of subjects, indicated short-term significance of progesterone cream in endometrial hyperplasia (6months or less) (103-105). Nonetheless, longer-term data of at least 12 months are required to support the adequacy of any progesterone formulation in protecting against the proliferative effect of estrogen on the endometrium (106). Several studies have shown that after using progesterone cream, serum progesterone levels were low and insufficient to inhibit the proliferative effect of estrogen on the endometrium (107-112) or induce secretory changes (110, 111). In addition, a longer term study of 48-weeks by Vashisht el al, failed to demonstrate the long-term efficacy of progesterone cream in preventing endometrial hyperplasia (113). At this time, the clinical use

of transdermal progesterone cream in endometrial hyperplasia is not recommended.

1.7.3 BHT and breast cancer

The risk of breast cancer with bioidentical hormone therapy is unclear. Several animal and cellular level studies suggest that estriol has a protective effect on the breast by blocking estradiol induced cell proliferation and possibly carcinogenesis (114-122). Similar to other estrogens, estriol has been shown to increase breast cancer cell growth (123-126).

Data from the WHI suggests a higher risk of breast cancer with EPT than ET. Yet the effect of synthetic progestins on the breast may be different from progesterone (35, 127-134), with observational data suggesting a lower risk of breast cancer with estrogen therapy (135). Further studies are still required to confer the beneficial effects of progesterone on the breasts.

1.8 Controversy over saliva testing

BHT promoters recommend hormonal saliva tests to customize BHT prescriptions to restore natural hormone balance. Followers of this practice also believe that saliva testing provides an accurate method of measuring the free bioavailable hormones. Yet researchers argue that due to the substantial inter-individual variability in saliva hormone levels, there is no standard balance of hormone levels that can be used to establish norms (136). Salivary hormone concentration varies with diet (137), time of day (138) and the specific hormone tested (139). Hence salivary assays show poor reproducibility and are poorly

correlated with serum hormones, proving it is an unreliable and invalid method of hormonal determination. (22, 140, 141). Furthermore, menopausal symptoms during the perimenopause are often the cause of fluctuating hormone levels; therefore, a single hormone level may not correlate with symptoms. Accordingly, the act of dosing a woman so her estrogen and progesterone levels achieve a specific target ratio known as "hormonal balance" is not supported by clinical data (142). Instead, hormones, mostly estrogen, should be adjusted based on symptom relief and to minimize side effects

1.9 Beliefs on BHT

Limited information is available on the attitudes and beliefs of health care professionals regarding BHT and the factors influencing these beliefs. In fact, there is a lack of studies about the beliefs of health care professionals about HT in general since the publication of the WHI. The only study we found was a survey of attitudes of Belgian gynaecologists toward HT (143). In 2003, Ena el al, found that, HT prescription attitudes of Belgian gynaecologists was not affected by the negative findings of the WHI (143). Included in their survey was a case study of a woman taking CEE and MPA for 2 or 11 years and no longer suffering from symptoms. Of the 577 respondents, 20% agreed to discontinue HT, over 60% recommended a different HT product, and 20% continued the same HT. The author attributed these findings to several reasons. First, many gynaecologists perceive other regimens, including different progestins, as still useful. Second, physicians, mainly in Europe, believe that the increased risk of cardiovascular events with HT in the WHI was due to the wrong choice of drug. Third, it was

suggested that some gynaecologists have difficulty in discontinuing a medication they have prescribed for years and there was a belief that HT improves the quality of life.

We were unable to identify any studies which specifically examined health care providers perceptions on BHT. The only studies we found on this topic were 2 cross-sectional surveys that assessed beliefs and experiences of women on BHT. In both studies, authors concluded that most women endorsed a belief that BHT is safer than other HT (50, 144).

Due to the lack of definitive evidence about the safety and efficacy of BHT, pharmacists may provide information to patients based on their personal beliefs or experiences with BHT. The information provided can greatly affect patients' perceptions and treatment decisions about BHT (145). Identifying these beliefs can help us understand the type of information currently communicated to patients about BHT and its role in clinical practice.

We recently completed a small pilot survey of 95 pharmacists in Edmonton (manuscript included in chapter two). In the survey, 41 % of respondents believed that BHT referred to only compounded hormones. Only half of respondents believed BHT's benefits and risks were equal to those of other hormone therapies, whereas a third (39%) believed that progesterone cream can be used to prevent estrogen-induced endometrial hyperplasia. Not surprisingly, beliefs about BHT and saliva testing, and confidence in BHT were significantly influenced by pharmacy compounding practice (146). Building on our experience

with the pilot project, we updated the survey tool and expanded the study to target a larger cohort of pharmacists in Alberta to assess beliefs about the safety and efficacy of BHT compared to other hormone therapy. A similar study is being planned in Nova Scotia to contrast differences in beliefs between the two provinces.

1.10 Research question and Objectives

1.10.1 Research Question

What do Alberta pharmacists believe about Bioidentical Hormone Therapy?

1.10.2 Objectives

1. To assess pharmacists' beliefs regarding the safety and efficacy of BHT compared to other HT.
2. To determine knowledge about the definition and classification of BHT
3. To identify Pharmacists' education and learning needs about BHT.
4. To identify pharmacists' confidence level in recommending and providing patient education about BHT
5. To determine factors influencing knowledge and beliefs about and confidence level in BHT.

CHAPTER TWO

PILOT STUDY

A Survey of Pharmacists' Beliefs on Bioidentical Hormone Therapy

2.1 Introduction

The use of hormone therapy (HT) to treat menopause symptoms has declined since the publication of the Women's Health Initiative (WHI) in 2002.[1-3] In Canada, the number of women using HT decreased at an average rate of 17% per year between 2001-2002 and 2006-2007.[4] Similarly, between January and June 2003, one study analyzing two nationally representative US databases reported a 50% decrease in all HT prescriptions.[5] Current guidelines recommend using hormone therapy (HT) to manage moderate to severe menopausal symptoms.[6,7] As a result of the outcomes of the WHI and safety concerns expressed in the lay press, health care professionals and patients have become more conservative with the use of HT, including a shift to the use of bioidentical hormones. Recent promotion of bioidentical hormone therapy (BHT) as a "safer alternative" in the media and by celebrities such as Suzanne Summers has caused even more confusion about the role of BHT.[8]

Unfortunately, there is much controversy surrounding the term "bioidentical hormones." A recent definition proposed is *"chemical substances that are identical in molecular structure to human hormones"*.[9] In the context of HT, these would include any product containing estradiol, estrone, estriol, progesterone, or testosterone. The term is often inappropriately used to refer to

compounded formulations only; however, many commercially available, FDA-approved HT products contain bioidentical hormones.[7,10] BHT is also erroneously promoted as being natural and thus may be perceived by consumers as being safer. Using the term "natural" to describe BHT is misleading as natural refers to the source, not the chemical structure.[11] In fact, bioidentical hormones cannot be considered truly natural, as plant-derived estrogens must be synthesized to obtain hormones identical to the human body.[11] Evidence that BHT is associated with better outcomes and fewer side effects compared to non-bioidentical HT is lacking.[12-15] At this time, the risks and benefits of BHT are assumed to be the same as with conventional HT.[7, 16, 17]

Custom BHT formulations can be compounded for a variety of administration routes including capsules, topical gels, and creams.[17] Common compounded BHT formulations include using estriol, the least potent of the estrogens, often in combination with estradiol (Bi-Est) or both estradiol and estrone (Tri-Est). Estriol is not commercially available in North America. Proponents of estriol promote it as having less risk of leading to breast cancer compared to other estrogens; however, there is a lack of good evidence to support this claim.[11,17-19] Transdermal progesterone cream is another commonly compounded HT. Transdermal progesterone cream may help relieve vasomotor symptoms;[20] however, should not be used with estrogens for endometrial protection.[7] Salivary hormone levels are also sometimes used to guide individualization of compounding BHT products and to adjust therapy.[14] The role of salivary hormone testing in this setting remains unclear.[14,15]

The controversy with BHT may prevent patients from receiving concise, balanced information on hormone therapy. Professional organizations have expressed concern that due to the highly publicized claims about BHT, women may be receiving potentially misleading or false information about the benefits and risks of BHT.[10,21,22] As there is a lack of conclusive evidence on the safety and efficacy of BHT, many health care providers may provide information to patients based on their own personal beliefs and experiences with BHT. Limited information is available on what health care professionals, including pharmacists, believe about BHT. The primary objective of this study was to assess the beliefs of pharmacists on the safety and efficacy of BHT in relation to other hormone therapy. Secondary objectives were to assess beliefs on specific BHTs (for instance, estriol and natural progesterone), to assess pharmacists' confidence in BHT, and to identify factors influencing pharmacists' beliefs.

2.2 Materials and Methods

2.2.1 Study design

This was a cross-sectional survey of community pharmacists practicing in Edmonton, Alberta, and surrounding areas. Pharmacists were stratified by pharmacy worksite including chain, independent, and compounding pharmacies. Surveys were distributed manually through direct visits to the pharmacies between November 2009 and March 2010. Pharmacists who provided written consent were asked to complete the written survey and submit directly to the study team member. The study was approved by the University of Alberta Health Research Ethics Board (November 9th 2009).

2.2.2 Survey instrument

The survey instrument was a 32-item, written, self-administered questionnaire with sections on demographics, knowledge of HT, and beliefs about and confidence in BHT. All survey questions were investigator-initiated and were close-ended. Questions compared the efficacy and safety of BHT to non-bioidentical HT, and estriol to other estrogens. Beliefs of efficacy were captured as 1 ="less effective," 2 = "equally effective," and 3 = "more effective." Similarly, beliefs about risks were categorized as 1 = "less risk," 2 = "equal risk," and 3 = "more risk." Beliefs in transdermal progesterone cream and saliva testing were measured on a 3-point scale with 1 = "agree," 2 = "neutral," and 3 = "disagree." A 5-point Likert scale where 1 = strongly disagree to 5 = strongly agree was used to assess confidence in BHT. The survey was pretested with two experts in the field for content and comprehensibility.

2.2.3 Data analysis

Summary statistics were used to describe the extracted data and characterize the cohort. Demographic factors assessed for association with beliefs about BHT included gender, age group, years since graduating, highest degree completed, type of community practice, and if the pharmacists worked in a pharmacy that compounded BHT. Association between demographic factors and beliefs about BHT were assessed by Students t-test. For groups with multiple levels, the association was assessed with one-way analysis of variance (ANOVA) (e.g. age groups). Pearsons' correlation was used for associations between two continuous variables (e.g., beliefs about BHT and years since graduating). All analyses were

performed with SPSS18 (SPSS Inc., Chicago, IL). None of the surveys were unreadable. Statistical significance for all analyses was defined as $p<0.05$.

2.3 Results

2.3.1 Respondents characteristics

One hundred and thirty-four pharmacists were approached in 90 pharmacies. Of those, 95 pharmacists completed the survey for a response rate of 71%. Of the respondents, 65% were female, 33% were less than 30 years of age and 47% had graduated in the last 10 years. The majority of the respondents worked in chain pharmacies (84%) and15% worked in pharmacies that compounded BHT (Table 1).

2.3.2 Knowledge of hormone therapy and information sources

Overall respondents were knowledgeable about the role of hormone therapy (HT), with most respondents believing HT was indicated for moderate to severe vasomotor symptoms (96%) and vaginal dryness (92%). However, only 51% of respondents believed HT prevented factures (Table 2). More than 40% of pharmacists classified BHT as only compounded products, with only 35% classifying it as both commercial and compounded HT products (Table 2). Scientific journal (61%) and peer opinion/other health professionals (67%) were the most commonly used information sources to gain knowledge about BHT.

2.3.3 Beliefs on bioidentical hormone therapy

In response to beliefs on BHT, 54% believed BHT to be equally effective as non-bioidentical HT for vasomotor symptoms; however, 21% responded that they did not know (Table 3). Similarly, more than half of the respondents believed BHT had equal effects on the risk of cardiovascular disease, venous thromboembolism and breast cancer; with nearly a third responding that BHT had less risk of side effects. More than 50% of respondents believed that estriol had equal efficacy (60%) and risks (56%) compared to other estrogens. The results were very similar to beliefs on natural progesterone, with 55% of pharmacists agreeing that natural progesterone had equal side effects as compared to synthetic progestins. In response to a question about using compounded progesterone cream to provide endometrial protection when used with estrogens, nearly 40% agreed the combination can be used to prevent endometrial hyperplasia (Table 4). The majority of pharmacists (43%) responded that they did not know if it is possible to use saliva tests of hormone levels to titrate doses of BHT.

2.3.4 Confidence in bioidentical hormone therapy

Overall, respondents did not feel confident recommending BHT (mean 2.5 $\pm$ 1.3) or providing patient education about it (mean 2.6 $\pm$ 1.2). The majority of respondents also identified gaps in their knowledge (mean 4.1 $\pm$ 0.9) about BHT.

2.3.5 Factors associated with beliefs

The only demographic group with positive beliefs about BHT was that of pharmacists who worked in a pharmacy that compounded BHT. This group was more likely to believe that BHT had less risk than non-bioidentical HT ($p=0.002$), estriol compared to other estrogens ($p<0.01$). This group also believed that natural progesterone had less risk relative to synthetic progestins ($p<0.01$). Similarly, this group was more likely to agree that natural progesterone cream can be used to relieve vasomotor symptoms ($p=0.025$) and prevent endometrial hyperplasia when used in combination with estrogens ($p=0.001$). Additionally, these pharmacists were more likely to believe saliva testing could be used to adjust BHT dosing ($p<0.01$). Pharmacists who compound BHT were also more likely to have greater confidence scores regarding recommending and providing BHT education to patients ($p<0.01$).

2.4 Discussion

Only half the respondents in our study believed that BHT had equal efficacy and risks compared to non-bioidentical hormones. This was consistent with responses for beliefs about estriol and natural progesterone. Nonetheless, only a third of pharmacists were aware that BHT includes both compounded and commercial products. In addition, there were many "do not know" responses (nearly 20%) to survey questions. Furthermore, fewer than half the pharmacists felt confident recommending and providing patient education about BHT.

The variability in responses and the high "do not know" response rate from pharmacists is not surprising and highlights the confusion surrounding BHT. Current position statements from various professional organizations recommend that the benefits and risks should apply equally to all HT.[7] However, many proponents of BHT promote it as a safer alternative to other HT, which is often the message provided by the media or non-medical sources. With the lack of quality studies to support this claim, it is too early to make any strong conclusions. Interestingly, in our study nearly half the pharmacists identified the media or personal experience as an information source for BHT, highlighting the need for targeted education on evidence-based resources.

Beliefs about estriol compared to other estrogens mirrored the beliefs of pharmacists about BHT in general, with nearly a fifth of respondents believing estriol had less risk. Estriol is purported to be protective on the breast and the endometrium, but there is limited evidence to support this. In fact, similar to other estrogens, estriol has been shown to stimulate breast cancer cells and increase endometrial thickness.[18,19,23]

Similarly, nearly a fifth of pharmacists in our study believed natural progesterone to have less risk than synthetic progestins. Though too early to make specific conclusions, natural progesterone may have more beneficial effects on the cardiovascular system than synthetic progestins, as it does not adversely affect lipid profiles.[24] Large observational studies have also shown a trend towards lower breast cancer rates with natural progesterone compared to synthetic progestins.[25]

A disconcerting finding was that nearly 40% of pharmacists believed that transdermal progesterone cream could be used to prevent endometrial hyperplasia when used in combination with estrogens. There is limited evidence that topical progesterone creams protect the endometrium from unopposed estrogen.[7] Studies assessing a duration of use longer than 48 weeks have failed to show adequate endometrium protection.[26, 27] This is an area warranting further targeted education for pharmacists.

In our study, pharmacists were unclear about using saliva testing for BHT dose titration. This question generated one of the highest do-not-know response rates, more than 40%. This may reflect the uncertainty in the role of saliva testing in practice, especially when using it to adjust BHT doses.[15] Hormone levels can fluctuate in perimenopausal women; therefore, a single value may be difficult to interpret or relate to symptom experience. In practice, BHT doses are adjusted based on symptom relief or the experience of side effects, which may not always correlate with hormone levels.[11,17]

Pharmacists who worked in pharmacies that compounded BHT not only had differing beliefs about BHT compared to other pharmacists, but also expressed greater confidence when dealing with BHT. Overall they were more likely to report a belief that BHT, estriol, and natural progesterone were safer. They were also more likely to believe in the use of natural progesterone cream for endometrial protection and in saliva hormone testing for dosage adjustment. This is likely a reflection of their practice and greater experience with BHT, which may have influenced their beliefs about and confidence in BHT. Unfortunately

our study was not set up to look at the reasons for these beliefs. On a parallel note, in a survey of women attending a menopause clinic, women who had greater experience with compounded BHT reported a belief that it was safer.[28]

Our study had several limitations. First, self-reporting bias may be present as the sampling of pharmacists was not random. Nevertheless, we had a response rate of more than 70%, which is higher than what is typically seen for pharmacist surveys.[29] It is possible that direct visits to the community pharmacies may have helped improve our response rate. Second, the validity and reliability of the questionnaire were not explicitly tested; this can affect the accuracy and stability of the measurements. Moreover, because beliefs are intangible, complex constructs, measuring them by a single tool may lead to construct underrepresentation (e.g. the questionnaire tool might fail to capture important aspects of the construct). Third, our sample size was low and limited to practicing pharmacists in one jurisdiction in Alberta (community pharmacists in urban settings), which limits generalizability of findings to pharmacists practicing in other areas such as rural or other practice settings. However, in most aspects our sample was similar to the demographics of Alberta pharmacists such as gender and education, except for a slightly younger age group.[30] Because of these limitations, this study can be considered purely exploratory, though the results help uncover important practice issues with BHT.

2.5 Conclusion

Data on the safety and efficacy of BHT is unclear. This can produce a great deal of confusion for health care professionals, and for women looking at hormone therapy options. Pharmacists, in our study, had varying beliefs about and comfort in dealing with BHT, which were influenced by their practice with compounding BHT. Pharmacists are in an ideal position to help educate and guide woman in making evidence-based decisions about BHT. To support pharmacists with these activities, our findings highlight the need for targeted education not only on the definition of BHT, but also the available evidence on the efficacy and safety of BHT.

2.6 Tables

Table 1. Characteristics and Practices of Respondents

Characteristics	Respondents (n=95)
Sex, n (%)	
Male	33 (35)
Female	62 (65)
Age, n (%)	
20-29 years	31 (33)
30-39 years	25 (26)
40-49 years	26 (27)
0ver 50 years	13 (14)
Mean years since graduation, y ±SD	14.0 ± 10.8
Highest degree completed, n (%)	
Baccalaureate Degree in Pharmacy	93 (98)
Master's Degree	1 (147)
Doctor of Clinical Pharmacy (PharmD)	1 (147)
Current practice in community pharmacy, n (%)	
Chain store	80 (84)
Independent	7 (7)
Specialty compounding pharmacy	6 (147)
Primary care network[a]	3 (3)
Pharmacy compounds hormone therapy, n (%)	14 (15)

[a] Primary care network is a group of health care professionals working collaboratively with Alberta health services to provide primary health services to patients

Table 2: Knowledge of Respondents and Information Sources Used

Knowledge and information sources	Respondents (n=95)
Indications for hormone therapy, n (%)	
Moderate to severe vasomotor symptoms	91 (96)
Vaginal dryness	87 (92)
Prevent fractures	48 (51)
Do not know	2 (147)
Risks for hormone therapy, n (%)	
Cardiovascular disease	78 (82)
Stroke	84 (88)
Venous thromboembolism	90 (95)
Breast cancer	85 (89)
Do not know	1 (147)
Classification of bioidentical hormone therapy, n (%)	
Compounded hormones containing estriol, estrone, estradiol, progesterone only	39 (41)
Commercial hormones containing estradiol, estrone, or micronized progesterone only	3 (3)
Both commercial and compounded listed above	33 (35)
Any hormone therapy	7 (8)
Other	1 (147)
Do not know	10 (11)
No response	2 (147)
Information sources used, n (%)	
Scientific Journals	58 (61)
Peer opinion/ other health professional	64 (67)
Media	20 (21)
Personal experience	18 (19)
Other	12 (13)

Table 3: Respondents Beliefs on Bioidentical Hormone Therapy

Item	Less n (%)	Equal n (%)	More n (%)	Do not know n (%)
Beliefs on Efficacy				
I believe for the treatment of vasomotor symptoms, BHT is _____ effective compared to non-bioidentical hormones. (n =94)	8 (9)	51 (54)	15 (147)	20 (21)
I believe for the treatment of osteoporotic fractures, BHT is _____ effective compared to non-bioidentical hormones. (n =93)	14 (15)	42 (45)	4 (4)	33 (35)
I believe that estriol is _____ effective compared to other estrogens. (n= 93)	8 (9)	56 (60)	6 (147)	23 (25)
Beliefs on Risks				
I believe that BHT is associated with ____ risk of cardiovascular disease (stroke, MI). (n =94)	22 (147)	48 (51)	5 (5)	19 (147)
I believe that BHT is associated with ____ risk of venous thromboembolism. (n =94)	19 (147)	49 (52)	8 (9)	18 (19)
I believe that BHT is associated with ____ risk of breast cancer. (n = 94)	18 (19)	51 (54)	7 (7)	18 (19)
I believe that BHT is associated with ____ risk of side effects. (n =95)	28 (29)	48 (51)	8 (8)	11 (12)
I believe that estriol has____ risk compared to other estrogens. (n =93)	16 (17)	52 (56)	5 (5)	20 (22)
I believe that natural progesterone is associated with _____ risk compared to other progestins. (n =92)	20 (22)	51 (55)	2 (147)	19 (21)

Table 4: Respondents' Beliefs About Use of Transdermal Progesterone Cream and Saliva Testing

Item	Agree n (%)	Neutral n (%)	Disagree n (%)	Do not know n (%)
Transdermal progesterone cream can be used in the treatment of vasomotor symptoms. (n = 92)	23 (25)	22 (147)	24 (26)	23 (25)
Transdermal progesterone cream can be used for endometrial protection when used in combination with estrogens. (n = 92)	37 (40)	8 (9)	20 (22)	27 (29)
Saliva testing of hormone levels is useful in the dose titration of BHT. (n = 93)	17 (18)	15 (147)	21 (147)	40 (43)

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CHAPTER THREE

METHODS

3.1 Study design and participants

This was a cross-sectional web-based survey targeting practicing pharmacists in Alberta, Canada. Inclusion criteria included pharmacists on the clinical registry of the Alberta College of Pharmacists (ACP) who agreed to participate in practice-based research, and were willing to complete an online survey. Pharmacists who did not wish to be contacted for practice-based research were excluded from the study. The study was approved by the University of Alberta Health Research Ethics Board.

3.2 Research procedure

An email invitation to participate in the web-based survey was sent to a random sample of pharmacists who met the inclusion criteria. The list was generated by ACP through a random number generator and sent to the study investigators. The online survey was accessible for a six week period from May 27 to July 8, 2011, with email reminders sent each week to non-responders. In an aim to increase the response rate, an incentive in the form of a draw for one of two 8GB iPod touch was offered. Participants interested in entering the draw were asked to submit their names and email addresses, and answer a skill-testing question upon survey completion. The odds of winning were 1 in 200. As requested by ethics, participants were also given the opportunity to receive additional educational materials on bioidentical hormone therapy (BHT) upon

request. The survey was administered by Academic Information and Communication Technologies (AICT) at the University of Alberta. AICT designed the online version of the survey tool, sent out the email invitations and reminders on behalf of the investigators, collected and processed all the data, and provided the data in SPSS and Excel format to the investigators.

3.3 Questionnaire

A 54-item online self-administered questionnaire was developed by the study team containing both quantitative components (close-ended and Likert scale questions) and qualitative components (open-ended responses) (Appendix A). All survey questions were investigator initiated as a review of the literature failed to identify any previously published surveys on BHT. The survey contained 4 sections: 1) demographics and practice related questions, 2) knowledge on BHT, 3) beliefs about BHT, and 4) confidence level and learning needs. An open-ended question was included at the end for pharmacists to share their pharmacy practice experiences with BHT. The time estimated to complete the questionnaire was approximately 10-15 minutes.

3.3.1 Questionnaire sections and measures of constructs

3.3.1.1 Demographics and practice related questions

Participants were asked to state their gender, age, years of practice, year of graduation, pharmacy school of graduation, highest degree completed, type of pharmacy practice, hours of practice, practice setting, whether or not they work in

a pharmacy that compounded BHT, and the frequency of dispensing compounded BHT.

3.3.1.2 Knowledge on BHT

This section included questions on definition, examples, and classification of BHT. Knowledge on definition was measured on a three-item-subscale that participants rated "true/agree", "false/disagree", or "do not know/not sure" based on their extent of agreement to the proposed statements. Questions included: 1) bioidentical hormones are chemical substances that are identical in molecular structure to human hormones, 2) bioidentical hormones are natural, meaning they are non-synthesized hormones, and 3) bioidentical hormones are natural, meaning they are extracted unaltered from plant sources. Agreement with question 1 and disagreement with questions 2 and 3 were interpreted as correct answers. Single items were used to identify participants' knowledge about examples and classification of BHT.

3.3.1.3 Beliefs about BHT

Beliefs were quantified using a 4-point multi-item Likert subscales anchored as "strongly disagree" to "strongly agree". A "do not know" response choice was also provided. Participants were asked to state their degree of agreement or disagreement with suggested items/statements constituting each of the following subscales:

- Beliefs about BHT efficacy compared to non-bioidentical hormones:

  Beliefs about BHT efficacy were assessed using a four- item-subscale, with items 1 and 2 measuring beliefs about BHT efficacy for the treatment of vasomotor symptoms and items 3 and 4 measuring beliefs about BHT efficacy for prevention of osteoporotic fractures.

- Beliefs about BHT risks compared to non-bioidentical hormones:

  Eight items were used to assess beliefs about BHT risks, with two items addressing each of the following risks: cardiovascular disease (CVD), blood clots, breast cancer, and side-effects.

- Beliefs about estriol efficacy and risks compared to other estrogens:

  Although this appeared as a set of four items in our questionnaire, beliefs about estriol efficacy and risks were quantified separately. Items 1 & 2 were used to assess beliefs about estriol efficacy and items 3 & 4 were used to measure beliefs about estriol risks.

- Beliefs about natural progesterone risks compared to synthetic progestins:

  Beliefs about natural progesterone risks were quantified using a set of three items to assess risk of side effects, cardiovascular adverse effects, and breast cancer.

- Beliefs about compounded progesterone cream:

  This section was composed of two items to assess beliefs on the efficacy of progesterone cream in: 1) treatment of vasomotor symptoms, and 2) preventing estrogen induced endometrial hyperplasia in a woman with an intact uterus.

- Beliefs about saliva testing

  A three-item subscale was used to measure participants' beliefs about saliva testing. Statements suggested saliva testing is useful in: 1) assessing hormone status, 2) determining the initial dose of estrogen and progesterone, and 3) BHT dose titrations.

3.3.1.4 Confidence level and learning needs

Confidence in recommending and providing patient education about BHT was measured using a two-item-subscale. Learning needs was captured on a single item.

3.4 Validity and reliability of questionnaire

The initial questionnaire was assessed for content validity by a small sample of pharmacists who are experts in the field (n=2) and then used in a pilot study of community pharmacists in Edmonton and surrounding areas (n=95). The questionnaire was revised based on the results of the pilot. The revised questionnaire was peer-reviewed by a small cohort of 11 pharmacists for face validity and comprehensibility. Those pharmacists were recruited from known

contacts and included pharmacists practicing in a variety of settings reflecting our study population. Cognitive semi-structured interviews were used to assess participants interpretations of the questions (147). The questionnaire was further revised based on participants feedback. For test-retest reliability, the survey was sent again to a random sample of 60 pharmacists two weeks after initial survey completion. Eight pharmacists completed the survey a second time. Convergent evidence of construct validity was provided by calculating Pearson's correlation coefficient of the beliefs and confidence scores with the frequency of dispensing compounded BHT. Internal consistency of different constructs (knowledge, beliefs and confidence) was measured using the Cronbach's alpha coefficient, providing further empirical evidence of the instrument's construct validity and reliability (148).

3.5 Sample size

Approximately 4200 pharmacists are registered on the clinical register in Alberta and the majority have agreed to be contacted for research purposes. Assuming a 95% confidence interval with a 5% margin of error, and a proportional variable of interest we needed 352 subjects in our study (149). We inflated the numbers to a sample size of 400 to account for partial completion of surveys. Based on previous experience, survey response rates for online surveys with pharmacists are often low (i.e. less than 20%) (150). For a 20% response rate, we decided to send invitations to 2000 pharmacists to achieve a sample size of 400.

3.6 Quantitative data analysis

All analyses were performed with SPSS18 (SPSS Inc., Chicago, IL). Descriptive statistics were used to describe the extracted data and characterize the cohort. Several variables were collapsed or combined in to new variables to be used as dependent measures in logistic/multiple linear regression analyses.

3.6.1 Creating outcome variables

3.6.1.1 Knowledge on BHT

The three items measuring knowledge on definition were combined creating a new dichotomous variable with two response categories: "good knowledge" (participants who answered all three items correctly, achieving the highest score of 6) and "poor knowledge" (participants with a total score<6). Before adding the items of this section, coding of item number 1 was reversed to allow for coding consistency (Appendix B).

3.6.1.2 Beliefs about and confidence in BHT

For subscales measuring beliefs about BHT and estriol, coding of all even items was reversed to ensure that all items were coded in the same direction. Subscales of beliefs and confidence demonstrated acceptable to excellent internal consistency with Cronbach's alpha values running from >0.7 to >0.9 (Appendix B) (151-153). For all subscales, items were combined and divided by the total number of items for subscale total scores, creating eight continuous dependent variables with score(s) running from 1 to 4. The dependent variables were as

follows: 1) beliefs about BHT efficacy in vasomotor symptoms, 2) beliefs about BHT efficacy in osteoporosis, 3) beliefs about BHT risks, 4) beliefs about estriol efficacy, 5) beliefs about estriol risks, 6) beliefs about natural progesterone risks, 7) beliefs about saliva testing, and 8) confidence in recommending and providing patient education about BHT. Other dependent variables included beliefs about the efficacy of compounded progesterone cream in relieving vasomotor symptoms and preventing endometrial hyperplasia.

The scores can be interpreted as follows:

- Beliefs about the efficacy of BHT and estriol:

  Higher scores indicated agreement with the equal efficacy of BHT compared to non-bioidentical hormones and estriol compared to other estrogens. Lower scores suggested that the respondent believed BHT or estriol to be more efficacious.

- Beliefs about the risks of BHT and estriol

  Higher scores indicated agreement with the equal risks of BHT compared to non-bioidentical hormones and estriol compared to other estrogens. Lower scores suggested that the respondent believed BHT and estriol had less risk.

- Beliefs about the risks of natural progesterone

  Higher scores indicated agreement with the less risk of natural progesterone compared to synthetic progestins.

- Beliefs about the efficacy of compounded progesterone cream

  Higher scores indicated agreement with the efficacy of compounded progesterone cream for relieving vasomotor symptoms and for preventing estrogen induced endometrial hyperplasia.

- Beliefs about saliva testing

  Higher scores indicated agreement with the use of saliva testing for hormonal assessments and BHT dose titrations.

- Confidence in BHT (confidence in recommending and providing patient education about BHT)

  Higher score indicated agreement with feeling confident providing recommendation on and patient education about BHT.

3.6.2 Independent variables

All independent variables were dichotomized to derive stable models (154) and for the ease of interpreting and reporting statistical results. These variables included: gender (male vs. female), age (≥30yr vs. <30yrs), years of practice (>10yrs vs. ≤10yrs), pharmacy school of graduation (University of Alberta vs. other), type of practice (community vs. other), practice hours (full-time vs. part-time), practice settings (urban vs. rural) and BHT compounding practice (work in a pharmacy that compounds BHT vs. do not work in a pharmacy that compounds BHT).

3.6.3 Multivariate analyses

Knowledge on the definition of BHT was analyzed by logistic regression. Factors associated with beliefs and confidence were examined by multiple linear regression. One logistic regression model and 10 multiple linear regression models were conducted using purposeful selection methods. In the purposeful selection method, the researcher controls each step of building the model as opposed to stepwise backward and forward procedures that are executed by statistical software. Steps of the purposeful selection procedure include: 1) checking for collinearity by determining the variance inflation factor (VIF), 2) fitting univariate regression models of several independent variables with the dependent variable, entering variables significant at $p<0.2$ and dropping the rest, 3) fitting a multivariate regression model of significant independent variables and dropping variables insignificant at $p<0.05$, and 4) checking for the confounding effect of insignificant variables before removing them from the final main effect model. All "do not know" responses were excluded from the multivariate analyses.

3.6.4 Comparisons by BHT compounding practice

Chi-square tests were used for discrete variables to compare characteristics of pharmacists who work in a pharmacy that compound BHT with those who do not work in a compounding practice.

3.7 Qualitative analysis

Qualitative data analysis was conducted using phenomenological approach employing content analysis (155). The pharmacists' written comments were initially reviewed separately by two investigators to identify emerging themes and agreement was reached by consensus.

CHAPTER FOUR

RESULTS

4.1 Demographics and practice related characteristics

The email addresses for 2000 randomly selected pharmacists were received from ACP, of which we excluded two individuals; one was a member of the study team and the other was a pharmacist we knew from a previous study who was not interested in participating in surveys. In all, 401 pharmacists completed the online questionnaire for a response rate of 20%. Table 5 summarizes the participants' demographic characteristics. Respondents were mainly female (64%), above 30 years of age (81%) and had been practicing pharmacy for more than 10 years (63%). The majority of pharmacists worked in community pharmacies (61%), in an urban setting (80%) and were full-time (73%) (Table 6). Among pharmacists who completed the survey, 17% worked in a pharmacy that compounded bioidentical hormone therapy (BHT), and 12% dispensed compounded BHT 1-2 times per month.

Demographics and practice related characteristics of our sample including gender, age group, and hospital practice were similar to Alberta pharmacists (156) (Table 7).

4.2 Knowledge and classification of BHT

The majority of respondents correctly agreed that bioidentical hormones are chemical substances that are identical in molecular structure to human hormones (67%); however more than 40% of respondents believed that bioidentical

hormones were natural and non-synthesized (43%), as well as extracted unaltered from plant sources (42%) (Table 8). Respondents overall demonstrated good knowledge on examples of bioidentical hormones, with most participants responding that estradiol, estriol, estrone and progesterone are examples of bioidentical hormones, and 60% selecting all four as examples of bioidentical hormones. However, only 35% correctly classified BHT as including both commercial and compounded HT products, while 38% of respondents classified BHT as being primarily compounded HT products (Table 9).

4.3 Pharmacists beliefs

4.3.1 Beliefs about BHT

Respondents' beliefs about the efficacy of BHT are found in Table 10. Overall 68% of respondents agreed that BHT is as effective as non-bioidentical hormones for treating vasomotor symptoms. Nevertheless, 22% believed BHT is more effective for treating vasomotor symptoms. More than half the respondents agreed BHT is as effective for preventing osteoporotic fractures (55%).

In regards to the risks of BHT, majority of respondents agreed that BHT had equal risk of cardiovascular disease (CVD) (60%), venous thromboembolism (VTE) (64%), breast cancer (60%), and side effects (57%) as compared to non-bioidentical hormones. However, nearly a quarter of respondents agreed that BHT had less risk of side effects as compared to non-bioidentical hormones.

4.3.2 Beliefs about estriol, natural progesterone and compounded progesterone cream

Responses to beliefs about estriol and natural progesterone, were varied with many do not know responses (30% to 42%). Just over half of the respondents agreed that estriol is as effective as other estrogens in treating vasomotor symptoms (54%) and had the same risks (52%) (Table 11). As many as 20% responded that estriol had less risk compared to other estrogens. Less than half of the respondents disagreed that natural progesterone had a lower risk of side effects (44%), cardiovascular adverse effects (49%), and breast cancer (48%), compared to synthetic progestins.

In response to beliefs about compounded progesterone cream, almost 60% of respondents agreed that it was effective for vasomotor symptoms. Only 18% disagreed with the statement on the efficacy of natural progesterone cream in preventing estrogen induced endometrial hyperplasia. More than 30% responded do not know (Table 11).

4.3.3 Beliefs about saliva testing

Beliefs about saliva testing varied greatly with only 32% disagreeing with the usefulness of salivary levels in determining initial dose of estrogen and progesterone (Table 12). In addition, questions on saliva testing had the highest do not know responses of more than 40%.

4.4 Confidence level and learning needs

Overall, respondents did not feel confident in recommending BHT (76%) or providing patient education about BHT (76%) (Table 13). The majority of respondents also identified gaps in knowledge (88%). The most common areas identified for further learning included the safety and efficacy of BHT (88%), patient education about BHT (80%), and saliva testing (76%) (Table 14).

4.5 Factors associated with BHT knowledge

Pharmacists who work in a pharmacy that compounds BHT were three folds more likely to have a good level of knowledge about the definition of BHT compared with pharmacists who do not compound BHT (OR=3.17, 95% CI 1.81-5.52, $p<0.001$). Additionally, the odds of having a good level of knowledge about the definition of BHT was twice as high for pharmacists working in an urban setting (OR=2.09, 95% CI1.08-4.04, $p=0.029$).

4.6 Factors associated with BHT beliefs and confidence

In multiple regression analyses, the only variables associated with beliefs with BHT was practice related characteristics including BHT compounding practice, type of practice, practice setting and years of practice (Table 15). Pharmacists who worked in a compounding BHT practice were more likely to agree that BHT had lower risks compared with non-bioidentical hormones (B= -0.57, $p<0.001$), and believe that estriol is more effective (B= -0.37, $p<0.001$) and had less risk (B= -0.55, $p<0.001$) than other estrogens. In addition, they were more likely to agree than natural progesterone had less risk (B= 0.67, $p<0.001$)

and that transdermal progesterone cream is effective in relieving vasomotor symptoms (B= 0.38, p<0.001) and providing endometrial protection against the effects of estrogen (B= 0.29, p= 0.007). Furthermore they were more likely to have positive beliefs about the use of saliva testing (B= 0.55, p<0.001) and had a higher level of confidence in recommending and providing patient education about BHT (B= 0.96, P<0.001). Pharmacists who worked in community pharmacies were more likely to believe that estriol is safer (B=-0.17, p=0.03), and saliva testing is effective for hormonal assessment and BHT dose titrations (B= 0.32, p= 0.009). They also had a higher level of confidence in recommending and providing patient education about BHT (B= 0.26, p= 0.001). Pharmacists who worked in urban settings were more likely to believe in the lower risk of natural progesterone (B= 0.20, p= 0.032), efficacy of compounded progesterone cream for vasomotor symptoms (B= 0.17, p= 0.036), and the use of saliva testing (B= 0.28, p= 0.03). Finally, pharmacists with more than 10 years of practice experience were more likely to believe that estriol is safer (B= -0.19, p= 0.012). No collinearities among independent variables were detected (VIF values <10).

4.7 Comparisons by BHT compounding practices

Demographics, practice related characteristics, knowledge and beliefs of pharmacists working in compounding BHT practice compared to those who do not is found in Tables 16. Pharmacists who compounded were more likely to be male (p= 0.023), have greater than 10 years of experience (p= 0.032) and work in the community (p<0.001). Knowledge on examples and classification of BHT were significantly higher among pharmacists who compound BHT (p<0.001).

4.8 Evidence of reliability and validity

Our tool was developed to measure various constructs such as knowledge of, beliefs about and level of confidence in BHT. Most of these constructs were measured on a multi-item scale. The uni-dimensional attributes of these scales were measured by Cronbach's alpha. All sections demonstrated acceptable to excellent internal consistency with Cronbach's alpha values ranging from >0.7 to >0.9, providing evidence for reliability and construct validity of our data collection tool (Appendix B). Further evidence of the tool reliability over time was provided by a test re-test reliability coefficient of 0.70 (157). Good convergent evidence of construct validity was established. Except for pharmacists' beliefs about BHT efficacy, all other beliefs show significant correlations with frequency of dispensing compounded BHT ($p<0.01$). Of these, beliefs on BHT risks, estriol efficacy and risks, natural progesterone risks and saliva testing demonstrated a moderate to good strength of correlation (r's 0.32-0.48) (158). Despite statistical significance, beliefs on compounded progesterone cream show poor convergence with frequency of dispensing compounded BHT. Confidence in recommending and providing patient education on BHT had the most evidence of convergence with compounded BHT dispensing frequency, with a correlation coefficient of nearly 0.6. Table 17 describes correlations between constructs and frequency of dispensing BHT.

4.9 Qualitative data analysis

In the survey, pharmacists were asked to share their experience with BHT. Major themes arising from the submissions were confusion about the term, and their lack of knowledge and need for further education in this area (Appendix C). Furthermore, through their written stories of BHT experiences, pharmacists were identified to have opposing opinions to the practice of compounding BHT, with pharmacists who practiced in the area being very favourable to compounded BHT and those who did not practice in the area having opposing views.

4.9.1 General themes

4.9.1.1 Confusion with term

Pharmacists felt that there is a lot of confusion surrounding the use of BHT. Some pharmacists expressed confusion with the definition of BHT and expressed the need for a proper definition.

> *"I don't have a specific definition of BHT which makes it difficult to answer the questions. I have two definitions. Any HRT that is not produced by the body naturally, or those that are defined by TV commercials as those that are naturally occurring and prepared to mimic hormone activity… We see increase in questions about BHT when it hits media, i.e. Suzanne Sommers and Oprah. I wish there were more clarification in what BHT really means so that the explaining [of] BHT is not as convoluted."*

In addition, some pharmacists indicated that they were hearing differing views on BHT and were confused with the contrasting information finding it difficult to make their own assessments about BHT.

> *"There are so many different articles and educational materials out there and it's hard to believe what is correct and what is not!"*

Adding to this was that a number of pharmacists felt that there was a lack of studies done on BHT. Furthermore, some pharmacists expressed that they did not feel adequately prepared to interpret the literature to be able to make an informed decision on BHT.

> *"I think that a session on evaluating the literature on BHT would be useful. [U]ntil I started my PharmD I was swallowing a lot of the case reports as being studies. For 15 years I compounded and dispensed and invested sums of money in getting educated about BHT and traditional HR therapies. As time went on I realized that a lot of the salivary hormone tests were very similar and usually it was not a hormone imbalance but usually a lifestyle imbalance. Once [I] had a refresher course on literature evaluation,[I] looked at it from a different angle and realized that the answer is not always a compounded BHT but can also be commercial HR that is estradiol and progesterone based."*

There was concern expressed that the public may also be confused with BHT because of these conflicting messages about the definition and safety of BHT.

Some pharmacists felt that the media messages often contained misinformation and were misleading. One pharmacist commented:

> *"Many women are interested in BHT. They have been led to believe, by advertising and even the term "BIOIDENTICAL", that BHT is safer than commercial products"*

Other pharmacists indicated that they felt it was their role to help and support patients even if they were not actively involved with BHT because of the misinformation being given to patients. For example:

> *"I have not been very involved in providing BHT to patients. Typically, if patients were interested I would support them in evaluating the research and recommend that they see pharmacists/physicians I know that practice in this area. Personally, I would like to see more research done regarding BHT. I think there is a lot of misinformation that is being given to patients."*

4.9.1.2 Lack of knowledge and need for education

For the most part, pharmacists reported they had no experience and lacked knowledge on BHT with many expressing interest in further education in this area. Pharmacists overall indicated they were knowledgeable about the benefits and risks of HT in general but were confused about the role of BHT.

"*I have never provided it to a patient in my practice thus far....I realize I do not fully understand the risks/benefits of Non-BHT vs. BH but understand the effects/risks/benefits of hormones in general*."

Several pharmacists emphasized the need for additional education and training in this area, especially with interpreting the available evidence on BHT, and knowing what were reliable resources for information on BHT. Some pharmacists for example commented*:*

"[M]y exposure to BHT is very limited. However, I do realize that many of my patients are older women and the potential to be asked questions on BHT or HRT in general is high. Therefore, this is an area that I definitely need to review and learn more about "

"*I feel my education was extremely lacking in this area and think it would be an excellent idea to expose students to the area of BHT. I want to learn more about BHT but don't know where to find reliable information regarding BHT"*

"*In my experience, however, there are some individuals with very strong beliefs for or against hormonal therapy and BHT. [I]t is important that pharmacists are equipped to address these beliefs with fact and information*".

4.9.1.3 Supportive of compounding BHT

Pharmacists who worked in pharmacies that compounded BHT were those pharmacists expressing support with this practice. They perceived BHT to offer a more holistic approach to menopause management. Some pharmacists indicated that BHT is compounded to provide the right balance of hormones and more closely mimic physiological delivery of sex hormones compared to commercial products.

> "*I liken it to a therapeutic approach that seeks to mimic normal human physiology and to correct the dysfunction that so often leads to menopause as we know it"*

They also, perceived menopause to be a hormonal imbalance that varies from one patient to the other and thus required customization to adequately individualize therapy. In addition, these pharmacists were more likely to believe that BHT was a safer alternative with less adverse events such as cardiovascular disease and breast cancer. The following quotes highlight these points:

> "*I believe there is a possibility that bio-identical hormones can be compounded to be more effective if only because in my experience BH supplementation therapy entails a holistic approach to menopause treatment…...Since we are mimicking the normal human physiology, in theory the incidence of many cancers should be less….. Too early to say that [e]striol is "the" treatment but certainly points to some very exciting possibilities especially since this fits within a clinical picture that*

indicates that either excess estradiol or insufficient estriol may at least increase the risk of certain hormone sensitive cancers."

"Getting the right balance of the BH, I believe can give you less side effects, and possibly less risks of CVD/clots. It is all about balance and finding what works for each patient. To me it makes sense that our bodies would respond better to something it makes naturally (BH) instead of a foreign substance."

However, this view was not shared by all pharmacists, with some indicating that even though they felt BHT to be effective, the safety of compounded BHT should be assumed similar to conventional HT.

"*I have some experience with BHT related products and compound them in various formulations. I feel confident in the effectiveness of BHT and I have had many patients do very well on BHT medications. However, I have not seen conclusive enough evidence to suggest BHT is safer and so I currently advise patients to evaluate them with the same risk as conventional HRT*"

A number of pharmacists perceived saliva testing as a useful tool for assessing hormonal deficiencies and achieving meaningful dose titrations, as illustrated in the following excerpt:

"*I use saliva testing for both initial and continuous dose monitoring for patients that choose to have this done. I consider myself very confident is assessing BHT for patients that choose this form of hormone therapy. I*

always get the patient to saliva test their levels (for those that can afford the testing) for proper dosing. I have been using saliva testing for the past 7 years and found it to be the most useful tool to use to monitor patient therapy."

However, few of these pharmacists indicated that saliva testing is only useful in assessing initial hormone levels but not dose titrations, pointing out that dose adjustments should only be based on patients' symptoms.

"Saliva testing MUST be used in conjunction with SYMPTOMS. I would NEVER do a re-test to titrate doses as there is no evidence to support this practice. As with commercially available products (BH and non-BH, treatment with compounded BH and dose adjustments should be made based on symptoms"

"Saliva testing is best suited for a general assessment of hormonal levels. Dosage is initiated at a low dose and titrated based on response. BHT suitability is best predicated by symptomology assessment."

Pharmacists commented that the quality of compounded BHT products varied greatly among different compounding pharmacies. They highlighted the variability in bases used in the compounded formulations, as well as the different types of measuring devices as potential issues impacting efficacy. As expressed by one pharmacist:

"Different bases result in different efficacies as well as the way these delivery systems are measured and applied. There are different delivery

systems that are available and trial and error is often used to find the optimal choice of product and delivery system for the patient along with follow up tests such as saliva and blood tests in addition to the desired outcome of the therapy."

Overall pharmacists who compounded BHT believed they had good knowledge about BHT. Many commented on seeking professional development to enhance their knowledge and skills in this area such as symposiums or workshops on BHT (e.g. sponsored by Professional Compounding Centres of America (PCCA) was commonly mentioned). Pharmacists perceived that other health care professionals, mainly physicians, lacked knowledge in the area, especially with regards to compounded products available, bases used in these formulations, and starting doses. Pharmacists perceived that their role was to assist physicians in prescribing compounded BHT. Some examples of comments include:

"…I have attended a number of workshops and symposiums on BHRT as a member of PCCA and use my expertise in this area to assist physicians who may be uncertain of where to begin when it comes to prescribing compounded hormone products."

"Patients want these products based on their own research. Some come in knowing what they want and others are gathering info. Md's (sic) seem happy to prescribe but often have little knowledge of products and will prescribe based on patient requests or our suggestions"

Pharmacists commented that having a compounding BHT practice enabled them to provide more comprehensive direct patient care. Pharmacists expressed a greater role in patients' assessment, monitoring, patient education, recommending treatment plans, follow-ups, and referrals to other health care providers. They expressed greater professional satisfaction because of this enhanced role.

"…we provide a consultation (where the patient explain symptoms, we gather information on past history, family history of cancer etc., nutritional information, and more) and based on symptoms and lab tests provide a written recommendation to the physician. We compound BH on site. We also send samples to an independent lab for quality assurance."

"I have extensive experience with BH, have taken additional courses thru (sic) PCCA and work in a compounding pharmacy where BH are compounded and dispensed daily. I've been involved with assessing patients for their need for hormone replacement and in providing suggestions to physicians for starting doses or just general info about compounding alternatives"

"…..I have found that compounding is a valued niche opportunity which has given me much professional satisfaction and provided many valuable and positive patient outcomes."

4.9.1.4 Not supportive of compounding BHT

Pharmacists who were not supportive of the BHT compounding practice were mostly pharmacists who did not work in a BHT compounding pharmacy. They often expressed uncertainty about compounded BHT, commenting that they offer little additional benefit over commercially available BHT products. Many of these pharmacists believed it to be a way for compounding pharmacies to make money as well as a large scam to profit from susceptible people. In addition, a number of the pharmacists were frustrated with the marketing of these products by compounding pharmacies.

> *"I believe the whole issue of BHT is largely a scam by independent pharmacies to profit from susceptible people. The sooner the whole issue of pharmacists compounding is stopped the better, not just for these products. Products generally don't exist for a good reason and women are being ripped-off (sic) by greedy pharmacists making out that they are something special compared to their colleagues."*

One pharmacist even expressed frustration over the reluctance by some compounding pharmacies to share information about their BHT formulations. Further highlighting the competitive nature of the business.

> *"A doctor wrote a script for BHT. We are a pharmacy who usually does not compound these products. The doctor did not specify what base to use for compounding. He gave me a really hard time for even calling him about it. He also indicated that he did not know what base it gets*

compounded into. I called a few local compounding pharmacies to see what they use and NONE of them would give me any suggestions."

Pharmacists frequently expressed the lack of evidence to establish the use of saliva testing in BHT dosing and perceived as just another way to market and promote compounded BHT products.

"I don't know if I have seen any scientific evidence with respect to saliva testing or if it's just a gimmick to promote BHT."

"*I currently feel that compounding BHT and saliva testing only have the purpose of making money for the people doing these things. I don't see a place for them in addition to currently available pharmaceutical grade BHT and blood testing…..my experience is that it costs a lot of money, there is little scientific evidence to support compounding BHT and doing saliva testing and that it is an area that seems to prey on women and men who are suffering from other health issues."*

Furthermore pharmacists expressed concerns about the quality of compounded BHT products formulated. Pharmacists believed that because these products lack federal regulation and standardization there may be a greater potential liability associated with its production and use.

"I was employed in a pharmacy that compounded BHT and felt very uncomfortable with some of the compounding methods used. I feel there should be more regulation and standardization in this area. I do not believe that everyone receiving BHT products are receiving the same

product. I think that some pharmacies are using this treatment as a "cash cow" without regard for the patient."

"I often wonder if these compounding druggists have ever considered the potential liability of these products that they are making themselves without quality control procedures in place."

Few pharmacists shared that even though they do not agree with the science behind compounding BHT, they will dispense it after purchasing from compounding pharmacies. However, a number of the pharmacists also mentioned that they try to provide balanced education for the patient.

We do not custom compound hormone products, but purchase them from a pharmacy who (sic) does. I have always been reluctant about doing this, as I do not trust either the science behind custom compounded hormones, and I cannot attest to the manufacturing processes of the pharmacy that we purchase from. In fact, I go to great lengths to talk patients out of purchasing such products. However, for women who are adamant and will not be swayed, we do provide these products"

4.10 Tables

Table 5: Demographic Characteristics of Respondents

Demographic characteristics	Respondents N = 401
Gender n (%)	
Male	143 (36)
Female	258 (64)
Age, n (%)	
Less than 30 yrs	69 (17)
30-39 yrs	122 (30)
40-49 yrs	105 (26)
50-59 yrs	86 (21)
60 yrs and over	16 (4)
No response	3 (1)
Year of Graduation, n (%)	
1960-1969	7 (2)
1970-1979	57 (14)
1980-1989	82 (20)
1990-1999	107 (27)
2000-2009	122 (30)
2010 or after	24 (6)
No response	2 (1)
School of Pharmacy Attended, n (%)	
University of Alberta	297 (74)
Other Canadian University	68 (17)
Foreign University	29 (7)
No response	7 (2)
Highest Degree Completed, n (%)	
Bachelor's degree	322 (80)
Residency	38 (10)
Pharm D	13 (3)
Master's Degree	22 (6)
PhD	2 (1)
Other	4 (1)

Table 6: Practice Related Characteristics of Respondents

Practice Related Characteristics	Respondents N = 401
Years of Practice, n (%)	
< 2 yrs	36 (9)
2-5 yrs	51 (12)
6-10 yrs	61 (15)
11-20 yrs	109 (27)
>21 yrs	144 (36)
Types of Practice, n (%)	
Community pharmacy	
Independent	81 (20)
Chain	73 (18)
Franchise	26 (7)
Grocery store	62 (16)
Hospital pharmacy	90 (22)
Long term care	12 (3)
Consultant	8 (2)
Academia	5 (1)
Primary care network	15 (4)
Other	28 (7)
No response	1 (<1)
Hours of Practice, n (%)	
Full-time	293 (73)
Part-time	90 (22)
Other	15 (4)
No response	3 (1)
Site of Practice, n (%)	
Rural	79 (20)
Urban<100000	90 (22)
Urban>100000	232 (58)
BHT Compounding Practice	
No	315 (79)
Yes	67 (17)
Don't Know	8 (2)
Not Applicable	10 (3)
No response	1 (<1)
Frequency of Dispensing compounded BHT, n (%)	
Never	297 (74)
1-2 times per month	49 (12)
1-2 times per week	25 (6)
1-2 times per day	9 (2)
>2 times per day	21 (5)

Table 7: Characteristics of Our Sample Compared to Alberta Pharmacists Population

Characteristics	Participants (N=401)	2007 ACP registrants (N=3444)[a]	P value
Gender, %			
Female	64	63	0.58
Age group, %			
<30 yrs	17	16[b]	0.51
30-39 yrs	30	31[b]	0.80
40-49 yrs	26	26[b]	0.93
>50 yrs	25	25[b]	0.84
Type of practice, %			
Community	61	75	<0.05
Hospital	22	20	0.22
Practice setting, %			
Urban	80	85	<0.05

ACP, Alberta College of Pharmacists

Note: one sample test of proportion was used for all comparisons

[a]Data from workforce trends of pharmacists for selected provinces and territories in Canada, 2007 (156)

[b]Approximate percentage from figures

Table 8: Responses on knowledge on BHT definition

Items	True (Agree) N (%)	False (Disagree) N (%)	Do not know (Not Sure) N (%)
BH are chemical substances that are identical in molecular structure to human hormones (N=397)	267 (67)	52 (13)	78 (20)
BH are natural, meaning they are non-synthesized hormones (N=392)	98 (24)	172 (43)	122 (30)
BH are natural, meaning they are extracted unaltered from plant sources (N=393)	67 (17)	167 (42)	159 (40)

Table 9: Responses on Examples and Classification of BHT

Item	Respondents N = 401
Responses on examples of BHT, n (%)	
Conjugated Equine Estrogens (CEE)	55 (14)
Estradiol	307 (77)
Estriol	280 (70)
Estrone	272 (68)
Progesterone	330 (82)
Medroxyprogesterone acetate (MPA)	30 (8)
Estradiol,estriol,estrone and progesterone	220 (60)
Responses on classification of BHT, n (%)	
Compounded hormones containing estriol, estrone, estradiol and/or progesterone	153 (38)
Commercial products containing estradiol or micronized progesterone	29 (7)
Both compounded hormones containing estriol, estrone, estradiol and/or progesterone and commercial products containing estradiol or micronized progesterone	139 (35)
Any hormone therapy product	19 (5)
Other	2 (1)
Do not know	59 (15)

Table 10: Beliefs About BHT Efficacy and Risks

Items	Strongly Disagree N (%)	Disagree N (%)	Agree N (%)	Strongly Agree N (%)	Do not know N (%)
Beliefs about efficacy					
BHT is as effective for the treatment of vasomotor symptoms (N=399)	7 (2)	35 (9)	224 (56)	48 (12)	85 (21)
BHT is more effective for the treatment of vasomotor symptoms (N=398)	27 (7)	168 (42)	67 (17)	21 (5)	115 (29)
BHT is as effective for the prevention of osteoporotic fractures(N=398)	15 (4)	54 (14)	169 (42)	31 (8)	129 (32)
BHT is more effective for the prevention of osteoporotic fractures (N=398)	29 (7)	163 (41)	42 (11)	13 (3)	151 (38)
Beliefs about risks					
BHT has the same risks of cardiovascular disease (N=400)	10 (3)	70 (18)	212 (53)	28 (7)	80 (20)
BHT has less risk of cardiovascular disease (N= 399)	26 (7)	190 (47)	71 (18)	16 (4)	96 (24)
BHT has the same risk of blood clots (N=398)	9 (2)	54 (14)	227 (57)	27 (7)	81 (20)
BHT has less risk of blood clots (N=398)	27 (7)	205 (51)	56 (14)	11 (3)	99 (25)
BHT has the same risk of breast cancer (N=397)	11 (3)	55 (14)	212 (53)	28 (7)	91 (23)
BHT has less risk of breast cancer (N=396)	25 (6)	199 (50)	43 (11)	19 (5)	110 (27)
BHT has the same risk of side effects (N=397)	12 (3)	86 (21)	201 (50)	28 (7)	70 (18)
BHT has less risk of side effects (N=398)	24 (6)	184 (46)	79 (20)	20 (5)	91 (23)

Table 11: Beliefs About Estriol, Natural Progesterone and Compounded Progesterone Cream

Items	Strongly Disagree N (%)	Disagree N (%)	Agree N (%)	Strongly Agree N (%)	Do not know N (%)
Beliefs about estriol					
Estriol is as effective in vasomotor symptoms (N=398)	8 (2)	35 (9)	200 (50)	14 (4)	141 (35)
Estriol is more effective in vasomotor symptoms (N=394)	17 (4)	163 (41)	41 (10)	6 (2)	167 (42)
Estriol has the same risks (N=398)	9 (2)	68 (17)	191 (48)	16 (4)	114 (28)
Estriol has less risks (N=396)	18 (5)	173 (43)	51 (13)	17 (4)	137 (34)
Beliefs about natural progesterone risks					
Natural progesterone has less risk of side effects (N=398)	13 (3)	164 (41)	96 (24)	31 (8)	94 (23)
Natural progesterone has less risk of cardiovascular adverse effects (N=398)	14 (4)	182 (45)	59 (15)	21 (5)	122 (30)
Natural progesterone has less risk of breast cancer (N=397)	15 (4)	177 (44)	59 (15)	15 (4)	131 (33)
Beliefs about compounded progesterone cream					
Natural progesterone cream efficacy in vasomotor symptoms (N=397)	7 (2)	65 (16)	208 (52)	27 (7)	90 (22)
Natural progesterone cream efficacy in endometrial hyperplasia (N=396)	14 (4)	55 (14)	178 (44)	23 (6)	126 (31)

Table 12: Beliefs About Saliva Testing

Items	Strongly Disagree N (%)	Disagree N (%)	Agree N (%)	Strongly Agree N (%)	Do not know N (%)
Salivary estrogen and progesterone levels is useful in assessing hormone status (N=400)	27 (7)	80 (20)	94 (23)	27 (7)	172 (43)
Salivary hormone levels is useful in determining initial dose of estrogen and progesterone (N=397)	30 (8)	97 (24)	60 (15)	22 (6)	188 (47)
Saliva testing is useful in dose titration of BHT (N=400)	30 (8)	93 (23)	71 (18)	17 (4)	189 (47)

Table 13: Confidence Levels on BHT Patient Education and Recommendation

Items	Strongly Disagree N (%)	Disagree N (%)	Agree N (%)	Strongly Agree N (%)	Do not know N (%)
I have identified gaps in my general knowledge of BHT that need strengthening (N=396)	6 (2)	25 (6)	178 (44)	178 (44)	9 (2)
I feel confident recommending BHT (N=399)	121 (30)	185 (46)	57 (14)	16 (4)	20 (5)
I feel confident providing patient education on BHT (N=399)	116 (29)	188 (47)	63 (16)	16 (4)	16 (4)

Table 14: Learning Needs on BHT

Learning needs on BHT	N (%)
Safety and Efficacy of BHT	351 (88)
Patient Education about BHT	321 (80)
Saliva Testing	306 (76)
Availability of Commercial BHT products in Canada	281 (70)
Compounding of BHT products	262 (65)
Other	16 (4)

Table 15: Factors Significantly Associated With Beliefs About and Confidence in BHT

Factors	B coefficient (95% CI)	T statistic	P value	Adjusted R^2
Beliefs about risks of BHT (N= 246)				0.16
Pharmacists working in BHT compounding pharmacies	-0.57 (-0.74, -0.41)	-6.92	<0.001	
Beliefs about efficacy of estriol (N= 192)				0.13
Pharmacists working in BHT compounding pharmacies	-0.37 (-0.50, -0.24)	-5.47	<0.001	
Beliefs about risks of estriol (N= 252)				0.19
Pharmacists working in BHT compounding pharmacies	-0.55 (-0.73, -0.36)	-5.78	<0.001	
Community pharmacy	-0.17 (-0.33, -0.02)	-2.182	0.03	
Years of practice (>10years vs. ≤10yrs)	-0.19 (-0.34, -0.05)	-2.55	0.012	
Beliefs about less risks of natural progesterone (N= 253)				0.18
Pharmacists working in BHT compounding pharmacies	0.67 (0.49, 0.85)	7.28	<0.001	
Urban settings	0.20 (0.02, 0.38)	2.152	0.032	
Beliefs about efficacy of compounded progesterone cream in vasomotor symptoms (N= 307)				0.08
Pharmacists working in BHT compounding pharmacies	0.38 (0.22, 0.55)	4.556	<0.001	
Urban settings	0.17 (0.01, 0.33)	2.107	0.036	
Beliefs about efficacy of compounded progesterone cream in preventing endometrial hyperplasia (N= 270)				0.05
Pharmacists working in BHT compounding pharmacies[a]	0.29 (0.15, 0.55)	2.74	0.007	
Beliefs about saliva testing (N= 204)				0.14
Pharmacists working in BHT compounding pharmacies	0.55 (0.29, 0.81)	4.229	<0.001	
Community pharmacy	0.32 (0.08, 0.55)	2.646	0.009	
Urban settings	0.28 (0.03, 1.58)	2.183	0.03	
Confidence in BHT[b] (N= 375)				0.28
Pharmacists working in BHT compounding pharmacies	0.96 (0.77, 1.15)	9.905	<0.001	
Community Pharmacy	0.26 (0.11, 0.25)	3.487	0.001	

95% CI, 95% confidence interval
[a]Type of practice was a confounder
[b]Confidence in recommending and providing patient education about BHT

Table 16: Classification of Demographics, Practice Related Characteristics, Knowledge and Beliefs by BHT Compounding Practice

Variables	BHT compounding practice		P value
	Pharmacists practicing in BHT compounding N = 67	Pharmacists who do not practice in BHT compounding N = 334	
Demographics[a], n (%)			
Gender-Male	32 (48)	111 (33)	0.023
Age- ≥30yrs	59 (88)	273 (82)	0.211
Pharmacy school of graduation-University of Alberta	53 (79)	244 (73)	0.302
Practice related characteristics[a], n (%)			
Years of practice ->10yrs	50 (75)	203 (61)	0.032
Type of practice- Community pharmacy	64 (96)	178 (53)	<0.001
Hours of practice-Full-time	46 (69)	247 (74)	0.373
Practice setting- Urban	51 (76)	271 (81)	0.346
Knowledge about BHT[a], n (%)			
Examples of BH			
Estrone, estradiol, estriol and progesterone	58 (87)	162 (49)	<0.001
Classification of BHT			
Both commercial and compounded HT[b]	44 (66)	109 (33)	<0.001
Beliefs about and confidence in BHT[c], Mean±SD			
Beliefs about BHT efficacy in vasomotor symptoms[d]	2.93±0.61	2.94±0.43	<0.001
Beliefs about BHT efficacy in osteoporosis[d]	2.80±0.53	2.86±0.42	<0.001
Beliefs about BHT risks[d]	2.36±0.70	2.93±0.46	<0.001
Beliefs about estriol efficacy[d]	2.56±0.45	2.93±0.34	<0.001
Beliefs about estriol risks[d]	2.23±0.74	2.86±0.52	<0.001
Beliefs about natural progesterone risks[e]	2.86±0.77	2.20±0.54	<0.001
Beliefs about efficacy of compounded progesterone cream in vasomotor symptoms[e]	2.82±1.14	2.76±0.57	<0.001
Beliefs about efficacy of compounded progesterone cream in endometrial hyperplasia[e]	3.06±0.57	2.71±0.67	0.007
Beliefs about saliva testing[e]	2.89±0.79	2.24±0.76	<0.001
Confidence in BHT[f]	2.83±0.76	1.76±0.65	<0.001

SD, Standard Deviation; [a]Chi-square analysis was used for examining univariate associations; [b]Both compounded hormones containing estriol, estrone, estradiol and/or progesterone and commercial products containing estradiol or micronized progesterone; [c]Results from multivariate regression analyses
[d]Higher scores reflect more agreement to equal efficacy/risks of BHT or estriol; [e]Higher scores reflect more agreement to less risk of natural progesterone, use of compounded progesterone cream in reducing vasomotor symptoms and preventing endometrial hyperplasia, use of saliva testing; [f]Higher score reflect more confidence in recommending and providing patient educatin about BHT

Table 17: Pearson's Correlation Coefficients of Different Factors With Frequency of Dispensing Compounded BHT

Constructs	Pearson's correlation
Beliefs about BHT efficacy in vasomotor symptoms	0.02
Beliefs about BHT efficacy in osteoporosis	0.05
Belief about BHT risks	-0.44[a]*
Belief about estriol efficacy	-0.32[a]*
Belief about estriol risks	-0.45[a]*
Belief about natural progesterone risks	0.48*
Belief about efficacy of progesterone cream in VMS	0.22*
Belief about efficacy of progesterone cream on EMH	0.23*
Belief about saliva testing	0.37*
Confidence in BHT[b]	0.56*

[a] negative correlation coefficient reflects convergence of high frequency of dispensing compounded BHT with low scores for beliefs on BHT risks and estriol efficacy and risks

[b]Confidence in recommending and providing patient education about BHT

*correlations significant at $p<0.01$(two tailed)

CHAPTER FIVE

DISCUSSION AND CONCLUSIONS

5.1 General discussion

Our study revealed that pharmacists' knowledge and beliefs about bioidentical hormone therapy (BHT) were very diverse, emphasizing the confusion surrounding the role of BHT. More than half of respondents believed BHT in general had equal efficacy and risks as non-bioidentical hormones. However, there were less agreement on the beliefs about estriol, natural progesterone, compounded progesterone cream, and saliva testing and a rise in "do not know" responses.

5.1.1 Knowledge on BHT

Overall, pharmacists were poorly informed about the definition of BHT, where only a quarter of respondents correctly defined bioidentical hormones and only one-third classified them as including both compounded and commercial HT products. One potential reason for this is that there is a lack of a consistent definition for BHT. In a recent literature review, over 60 definitions for BHT were identified from scientific literature and the lay press (43). Additionally, many of these definitions state that BHT is natural; and several define BHT as only customized/compounded preparations. The influence of the media and how these products are promoted may also play a part (159). Interestingly, half the pharmacists in our initial pilot study identified media and personal experience as information sources for BHT. Most promotional claims are for compounded BHT and often use the terms "natural", and "custom made", to imply the safety of these products over conventional HT. As demonstrated in the following quote from a website promoting compounded BHT:

"*A hormone is a hormone, no matter how it's made, right? Wrong! There are major, critical differences between synthetic hormones and natural bioidentical hormones. Natural hormones are much safer, more effective alternatives to synthetic hormones*" (160)

Majority of the pharmacists in our survey who worked in a BHT compounding pharmacy correctly identified examples of bioidentical hormones, and classified BHT as including both commercial and compounded products. In fact, they were 3 folds more likely to appropriately define BHT compared with pharmacists who did not compound BHT ($p<0.001$). As the nature of a professional's work heavily influences their knowledge seeking behaviour (161), pharmacists extensive roles with compounding BHT may have driven their urge to learn about BHT enhancing their knowledge.

5.1.2 Beliefs about BHT

Beliefs about the safety and efficacy of BHT were varied with many do not responses (20% to 40%), which further highlights the confusion about its use. Current position statements from various professional organizations such as the North American Menopause Society (NAMS), American Congress of Obstetricians and Gynaecologists (ACOG) and the Endocrine Society, state that the efficacy and risks of BHT is assumed similar to other HT (24, 59, 70). Nonetheless, BHT is often promoted by BHT advocates as a safer and more effective alternative to conventional HT. With the lack of scientific evidence to support these beliefs it's too early to make any conclusions.

5.1.2.1 Beliefs about efficacy

For the treatment of vasomotor symptoms, nearly 70% of pharmacists agreed that BHT has equal efficacy as compared to non-bioidentical hormones, with one-third indicating that it was more effective. This was consistent wih a theme arising from the written submissions by some of the pharmacists who were involved with BHT compounding, where they stated that superior efficacy can be achieved by getting the right balance of estrogen and progesterone used in BHT. Data on the efficacy of BHT for relieving vasomotor symptoms are available (71, 80), however superior efficacy has not been established (24, 59).

Beliefs about the efficacy of BHT for preventing osteoporotic fractures were even more varied, with a little over half of the respondents agreeing it had equal efficacy. This may be a reflection of pharmacists' opinions on the current role of HT for osteoporosis. Knowledge on the indications of HT in general was not captured in our Alberta wide survey, however, in our initial pilot study 96% of the respondents correctly indicated HT for moderate to severe vasomotor symptoms, whereas only half believed HT could be used to prevent osteoporotic fractures.

Approximately half of the pharmacists in our survey believed estriol had equal efficacy compared to other estrogens. Efficacy of vaginal estriol in improving climacteric symptoms has been demonstrated in several studies (71-75), however, data on the benefits of oral estriol in relieving menopausal symptoms have been mixed (76-79). Findings from uncontrolled and open label small-scale studies of poor methodological designs suggest the efficacy of oral estriol for the relief of climacteric complaints (78,

91). However, in a double blind, placebo controlled study by Lindsay et al, oral estriol was ineffective in controlling postmenopausal symptoms (76).

5.1.2.2 Beliefs about risks

Overall, 60% of the respondents believed BHT in general, had equal risks of cardiovascular disease (CVD), venous thromboembolism (VTE) breast cancer and side-effects. Nevertheless, almost a quarter believed BHT had less risk of CVD. This was further highlighted in the written comments by BHT compounding pharmacists where they expressed a strong belief about the lower CVD risk of BHT. This belief is often endorsed by BHT proponents who attribute the increase in cardiovascular events in the Women's Health Initiative (WHI), to the use of non-bioidentical hormones in the trial (35, 94). While, published data thus far suggest a more favorable effect on lipid profile with BHT (95, 97,162), it's unclear how this translates into a lower CVD risk. New randomized controlled trials (RCT's) such as the Kronos Early Estrogen Prevention Study (KEEPS) and the National Institute on Aging's Early versus Late Intervention Trial with Estradiol (ELITE), will attempt to provide more conclusive evidence for or against the cardio-protective effect of BHT (9,163).

Pharmacists' beliefs about the risk of BHT in general may have been influenced by their beliefs about natural progesterone risk. Twenty percent of the pharmacists believed that natural progesterone had less risk of CVD adverse effects compared to synthetic progestins. This mirrored pharmacists' beliefs about the less risk of CVD with BHT. Unlike medroxyprogesterone acetate (MPA), natural progesterone was shown to preserve the beneficial effect of estrogen on lipid profile (97, 164-167). Furthermore, several studies suggest the positive effects of natural progesterone on the cardiovascular system

through reducing the formation of atherosclerotic plaques and relaxing the vascular tone (95, 97, 164,168). Though the data looks promising, it is too early to say that natural progesterone is associated with less risk of cardiovascular disease. .

Pharmacists' beliefs about the less risk of CVD with BHT may also be affected by their views on different HT formulations. Transdermal HT has been associated with a lower risk of blood clots compared with oral formulations (169). In addition, unlike oral HT, transdermal HT products do not increase triglycerides levels. As all transdermal HT available in the market contain an estrogen that is bioidentical (17βestradiol), this may have influenced the way pharmacists may have responded. This was further demonstrated in the written comments by some pharmacists indicating that there was a difference in risks based on HT formulation. Unfortunately, our survey was not designed to capture this association.

One-fifth of the pharmacists also believed in the less risk of breast cancer with natural progesterone which is consistent with their beliefs' about the less risk of breast cancer with BHT in general. Natural progesterone may have different effects compared to synthetic progestins on breast cancer (64-66). Findings from a large cohort study following more than 80,000 women in France for 12 years, revealed an increased incidence of breast cancer among women using estrogen with synthetic progestins, that was not seen in women using estrogen with natural progesterone (135). While this may suggest a lower incidence of breast cancer with natural progesterone over synthetic progestins, more evidence is required to support the use of progesterone over other progestins (9).

Compared to other estrogens, half of the respondents believed estriol had similar risks; however 20% perceived estriol as safer. BHT compounding pharmacists were also more likely to express the superior safety of estriol in their written comments. BHT advocates believe that estriol, being the least potent estrogen has lower biological activity on the breasts and endometrium compared to other estrogens. The results of animal and *in vitro* studies suggesting that estriol blocks the cell proliferation induced by more potent estrogens on the breasts, are often quoted by BHT advocates as justification for the less risk of breast cancer (114-122).While estrogens' potency reflects on its binding affinity for estrogen receptors (170) it does not predict biological activity (171). Biological activity is rather affected by several factors such as type of estrogen receptors activated, estrogen-induced change in the receptors, and cellular expression of coactivators (170-172). In fact similar to other estrogens, estriol has been shown to stimulate breast cells proliferation (123-126). Furthermore, estriol has been shown to induce endometrial hyperplasia (77, 98, 100, 102,173-175) and potentially increase the risk of endometrial cancer if not used with progesterone (176).

5.1.2.3 Beliefs about compounded progesterone cream

Progestogens are primarily indicated for menopausal women with an intact uterus to negate the proliferative effect of systemic estrogen on the endometrium (24). Half of the pharmacists in our study believed that transdermal progesterone cream could be used for this indication, however, it is unclear if transdermal progesterone cream provides adequate levels to provide endometrial protection and there is wide variability with levels among women (83, 107-113). The anti-proliferative effects of progesterone cream have been shown in a short term study of 4 weeks duration (103), however longer term studies

of 48 weeks have shown inadequate protection (102). Discrepancies in levels may be attributed to differences in formulations (165). More long term RCT's are required before recommending transdermal progesterone cream for this indication.

5.1.3 Beliefs about saliva testing

Majority of pharmacists were unclear about the role of saliva testing in assessing hormone status and titrating BHT doses, with one of the highest do not know responses by nearly half of the respondents. Pharmacists expressed different beliefs about saliva testing in their shared experiences with BHT. Pharmacists who work in a BHT compounding pharmacy often indicated positive beliefs on saliva testing.

Saliva testing is often used in BHT compounding practice, in the belief that it is the ideal method to assess the free levels of serum hormones. Accordingly, menopausal women are assessed for hormonal deficiencies and "hormonal balance" is restored through individualized therapy. Although this approach seems sensible, it lacks scientific justification. Salivary assays show poor reproducibility and are poorly correlated with serum hormones which undermines the clinical usefulness of such testing (22, 140, 141). Moreover, hormone levels can fluctuate in the perimenopausal woman, therefore, a single value may be difficult to interpret or relate to symptom experience. In practice, BHT doses are adjusted based on symptom relief or the experience of side effects, which may not always correlate with hormone levels (26, 52).

5.1.4 Confidence with BHT

Not surprisingly, most of the pharmacists in our survey did not feel confident recommending BHT and providing patient education on BHT (76%). Over 80% felt they needed to learn about the safety and efficacy of BHT and patient education. Furthermore, from their written submissions, majority of pharmacists emphasized their need for additional education and training on BHT, and many felt obligated to provide patients with unbiased evidence based information on BHT.

5.2 Pharmacists' practice and beliefs

Pharmacists' working in a pharmacy that compounds BHT, were more likely to believe in the safety of BHT, efficacy and safety of estriol, safety of natural progesterone, efficacy of compounded progesterone cream and use of saliva testing in assessing hormonal status and in BHT dose titration. These beliefs are consistent with common claims by proponents of compounded BHT and how these are promoted, and were further highlighted by pharmacists' comments in the open-ended section of our questionnaire. Pharmacists compounding BHT expressed more favorable beliefs toward BHT, primarily to compounded products, stating that they can be custom tailored to provide superior efficacy and safety. They shared stories of positive patient outcomes with compounded BHT which added to their confidence in these products.

It's possible that these beliefs were influenced by their extensive role and experience with BHT. Studies in other practice areas have shown that level of experience and familiarity with certain therapies can influence beliefs of health care professional on these therapies (143,177). For example, a study looking at the attitudes of different health care

providers in oncology toward complementary therapies for cancer, showed that the health care providers who had the greatest familiarity, as well as provided a supportive role for patients using complementary therapies had more positive beliefs towards complementary therapies and believed in their safety (177). We were unable to identify a comparable study in health care professionals with BHT, however similar findings on beliefs were seen in a survey of women attending a menopause center (144). In the study by Iftikhar et al, women who had greater experience with compounded BHT reported a belief that it is safer than conventional HT (144).

Pharmacists' extensive role with BHT might have further influenced their beliefs through affecting the type of information they receive on BHT. Results from our qualitative analysis showed that pharmacist compounding BHT were more likely to search for additional training on BHT, and often indicated that they were trained through the Professional Compounding Centers of America (PCCA). PCCA provides training, recipes and raw ingredients for compounding BHT (178). These courses are often hosted by BHT advocates who may not always provide a balanced approach on the safety and efficacy of BHT. Beliefs of pharmacists in BHT compounding practice may be biased by the type of education they are receiving on BHT.

5.3 Insights from qualitative analysis

5.3.1 Challenges expressed by pharmacists

In their written stories, pharmacists expressed concerns with the conflicting evidence on BHT and that they were challenged in making informed decisions with the use of BHT. Adding to this challenge was that pharmacists felt they lacked the skills to adequately evaluate the literature in this controversial area. Pharmacists expressed the need for more training on how to interpret the literature to avoid providing misinformation to patients about BHT and to support them with treatment decisions.

5.3.2 Opposing views on compounding BHT practice

Interestingly, our study suggests that pharmacists have strong opposing views on compounded BHT based on their experience with this practice area. Common themes arising from pharmacists who compound BHT were that they believed it offered a more holistic approach to managing menopause and had a better safety profile. In addition, they felt that this practice prompted their professional development needs, and enhanced their professional role in patient care which gave them professional satisfaction. On the contrary, other pharmacists felt compounding BHT was just a “money-making” scheme and offered no advantage over commercial BHT. Furthermore, there was the perception that the practice of promoting compounded BHT by some pharmacists was detrimental to the image of other pharmacists who are not involved in compounding BHT.

5.4 Limitations

A few limitations to this study should be stated. First, the response rate to our online survey was low (20%). It's possible that respondents were biased towards or against BHT. Nonetheless, this was the response rate we were targeting to meet our sample size based on response rates of previously published studies with pharmacists surveys (151). Furthermore, the characteristics of our sample were very similar to Alberta pharmacists (156), other than a slightly lower percentage of pharmacists working in community practice (61% vs. 75%) and in urban settings (80% vs. 85%). Second, as this was a cross-sectional survey it only allowed for determining associations and generating hypotheses but not for assessing causality. For example, the study helped to reveal potential predictors for knowledge on, beliefs about and confidence in BHT. Third, our test re-test reliability may have been underestimated by the low response rate (13%) to the second survey administration, and the relatively long time frame allowed for survey completion (up to 2 months). Nonetheless, our survey demonstrated good evidence of reliability over time ($r=0.70$). Fourth, pharmacists' beliefs may have been influenced by the type of information they are receiving on BHT. Since we did not include a question looking at information sources on BHT, the association was not assessed quantitatively. Also, in our survey questions we used the term BHT vs. compounded BHT to assess general beliefs about BHT (and not just about compounded formulations), however, some pharmacists may have responded with the belief that the term BHT includes only compounded products. Finally, another limitation is the poor criteria used for providing convergence evidence of construct validity. In convergent validity the newly developed tool for measuring constructs (e.g. beliefs) should be correlated to a valid existing criterion.

However, failing to identify any previously used criterion for assessing beliefs, led us to create our own by asking participants how frequently they dispense compounded BHT. Nevertheless, this question may not be reflective of participants' beliefs on BHT since it was specific to compounded BHT. Perhaps, that is why it was not significantly correlated with beliefs on BHT efficacy and was poorly correlated with beliefs on progesterone cream efficacy. Yet, it has shown moderate to good evidence of convergence with all other beliefs (r's 0.32-0.56).

5.5 Comparison of results with the initial pilot study

Interestingly, findings from this study were very consistent with the results from our pilot data. For example in our pilot study half of the pharmacists' believed in the equal efficacy and safety of BHT; there were many do not know responses to survey questions (20%); and beliefs were influenced by BHT compounding practice. However, results from this study were better supported, by the methodology employed in sample selection and measurement of constructs. In our pilot study, the sample was not randomized and included only community pharmacists practicing in Edmonton and surrounding areas, recruited through direct pharmacy visits. Pharmacists in our main study were recruited from different practice settings all over Alberta and randomization was used for sample selection. A larger sample size was achieved in our main study, with sample characteristics more representative of pharmacists in Alberta. In addition, constructs were measured on a multi-item subscales, and validity and reliability of the survey tool were explicitly measured. Also, more valid and precise estimates of significant associations were determined by employing multivariate analyses. Furthermore, experiences with BHT were further identified using an open ended section.

5.6 Practice implications

Our findings have implications for educators, professional organizations and policy makers. Majority of pharmacists identified gaps in their BHT knowledge and emphasized the need for additional education in their written comments. In fact, after completion of the survey, 20 respondents contacted the study investigators, requesting additional educational materials on BHT. A number of these pharmacists also inquired about educational programs on this topic. The most common areas identified for further learning included safety and efficacy of BHT, patient education on BHT, saliva testing and evidence based medicine. Continuing pharmacy education (CE) providers, such as academic CE providers (e.g. Practice Development at the Faculty of Pharmacy and Pharmaceutical Sciences at the University of Alberta) or professional associations (e.g. Alberta Pharmacists Associations, Canadian Pharmacists Association) can use the findings to design educational curricula around these identified learning needs (179). For example, one area expressed by pharmacists as a learning need was the ability to interpret the literature and make decisions for patients, especially in a controversial area where there is a lack of quality studies. Practical reviews on interpreting the literature should be incorporated into sessions focusing on HT.

Designed educational curricula could also be implemented at a university level by integrating BHT topics into undergraduate pharmacy courses.

Furthermore, practice tools can be developed around the area of BHT to support pharmacists in their practice. One example of a practice tool in this area is the "Menopause Assessment Tool" recently published in the Canadian Pharmacists Journal (180). Practice tools in menopause may translate to changes in pharmacists' practice (181).

These results may be useful for professional organizations such as the Canadian Menopause Society (SIGMA), NAMS and the Society of Obstetricians and gynaecologists of Canada (SOGC), as well as policy makers. SIGMA is a multidisciplinary group recently set up with the mission to provide education initiatives and knowledge transfer on the area of menopause, and they are currently in the process of developing educational materials for patients and health care professionals. One of the topics could be on BHT, which could be provided to community pharmacists to distribute to patients. NAMS and SOGC develop guidelines or position statements on menopause and hormone therapy. Even though BHT has been briefly addressed in the NAMS 2010 HT position statements, BHT was barely discussed in the most recent SOGC guidelines (9). The results of our study indicate the need for more focus on the role of BHT in these guidelines. Regulatory measures can also be considered by provincial and federal policy makers. For example in the US, the FDA issued letters warning certain compounding pharmacies that they make false or misleading claims about their compounded BHT products. They were also notified that they may not compound drugs containing estriol unless they have a valid investigational new drug application (182).

5.7 Conclusion

The lack of conclusive data on the safety and efficacy of BHT poses a great deal of confusion for health care professionals looking at hormone therapy options. The diversity in beliefs among pharmacists in our study is only a reflection of this controversy. Findings from our study highlight the varying beliefs that pharmacists had about BHT that was influenced by BHT compounding practice. Our study identified areas for targeted education and practice tools development. Pharmacists can play a role to help educate and guide women in making informed decisions about BHT.

5.8 Future directions

Further directions include assessing the beliefs of other health care professionals involved with BHT such as physicians and nurses. Furthermore, patients' attitude toward the safety and efficacy of BHT should also be identified to get a better picture of their beliefs and the type of information they are receiving on BHT.

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Appendix A: Survey Tool

Title of Research Study: Pharmacists' Belief on Bioidentical Hormone Therapy

You have been asked to participate in a study to assess your beliefs regarding bioidentical hormone therapy (BHT). Participation in this study is completely voluntary. You are free to withdraw from the study at any time. You may choose to refrain from answering any questions you do not feel comfortable answering.

If you agree to participate in this study you will complete an online survey that should take approximately 10-15 minutes. You will be asked about your knowledge on BHT, beliefs on BHT safety and efficacy, education and learning needs on BHT and your comfort level in educating patients on BHT. You will also be asked questions to gather background information such as age, gender, practice environment and level of education.

All information collected from you will be anonymous and data presented will be summarized in aggregate form**. No individual information will be divulged. This information will be kept strictly confidential. Only the investigators will have access to your survey data. Your name will not be linked to any information you provide.** An overview of the results of the study will be presented at educational meetings and in written articles that will be published in professional journals.

As an incentive for participating in the study, you can enter in a draw to win one of two 8 GB ipod touch ($250 each). The odds of winning are 1 in 200. To participate in the draw, you will be asked to submit your name and email, and answer a skill-testing question, upon survey completion. Identifying information gathered for the purpose of the draw will be kept separate from your survey results and will only be used for the draw. Please note that identifying information will be destroyed after the draw is complete.

Paper copies will be made available upon request if you prefer to complete the survey in this manner.

For more information, please read the attached information letter. If you have concerns about your rights as a study participant, you may contact the Health Research Ethics Board (HREB) at the University of Alberta at 780-492-0302. This office has no affiliation with the study investigators.

Please contact Dr. Nesé Yuksel at 780-492-4442 if you have any questions or concerns.

Consent to participate is implied by completion of the survey.

Thank you in advance for your time and valuable input

Please check the answer that best describes what you feel. You are under no obligation to complete any or all of the items on the survey, however complete answers will be most helpful with this research. You may leave answers blank if you do not feel comfortable answering the question.

Section 1: General information about yourself and your practice

1. Gender:

☐ Male
☐ Female

2. My age is:

☐ less than 30 years
☐ 30-39 years
☐ 40-49 years
☐ 50-59 years
☐ 60 years and over

3. How many years have you been a practicing pharmacist?

☐ < 2 years
☐ 2-5 years
☐ 6-10 years
☐ 11-20 years
☐ ≥ 21 years

4. When did you graduate from pharmacy?

☐ 1959 or before
☐ 1960-1969
☐ 1970-1979
☐ 1980-1989
☐ 1990-1999
☐ 2000-2009
☐ 2010 or after

5. I got my bachelor degree in pharmacy from:

☐ University of Alberta
☐ Other Canadian University (please specify) _____
☐ Foreign University (please specify) _____

6. What is your highest degree completed?

☐ Bachelor's degree
☐ Residency
☐ PharmD
☐ Master's degree
☐ PhD
☐ Fellowship
☐ Other: _____

7. Which of the following best describes your primary work setting?

☐ Community pharmacy (please specify):
☐ Independent
☐ Chain
☐ Franchise
☐ Grocery store
☐ Hospital pharmacy
☐ Long term care
☐ Consultant
☐ Academia
☐ Primary care network
☐ Other: _____

8. What best describes your primary work setting?

☐ Part-time
☐ Full-time
☐ Other _____

9. What best describes your practice setting?

☐ Rural
☐ Urban <100 000
☐ Urban >100 000

10. Does your primary work setting compound estrogen/progesterone bioidentical hormone therapy (BHT)?

☐ Yes
☐ No
☐ Don't Know
☐ Not applicable

11. How frequently do you dispense compounded bioidentical hormones?

☐ Never
☐ 1-2 times per month
☐ 1-2 times per week
☐ 1-2 times per day
☐ >2 times per day

Section 2: Knowledge on Bioidentical Hormone Therapy (BHT)

12. Please indicate if you believe the following statements about estrogen/progesterone bioidentical hormones (BH) are True, False, or if you Do Not Know/Are Not Sure.

	True (Agree)	False (Disagree)	Do Not Know/Not Sure
BH are chemical substances that are identical in molecular structure to human hormones.	○	○	○
BH are natural, meaning they are non-synthesized hormones.	○	○	○
BH are natural, meaning they are extracted unaltered from plant sources.	○	○	○

13. Which of the following are examples of bioidentical hormones (BH)? (check all that apply)

☐ Conjugated equine estrogens (CEE)
☐ Estradiol
☐ Estriol
☐ Estrone
☐ Progesterone
☐ Medroxyprogesterone acetate (MPA)

14. Which of the following do you consider to be classified as bioidentical hormone therapy (BHT)? (check all that apply)

☐ Compounded hormones containing estriol, estrone, estradiol, and/or progesterone.
☐ Commercial products containing estradiol or micronized progesterone.
☐ Any hormone therapy product
☐ Other: _____
☐ Do not know

Section 3: Beliefs on Bioidentical Hormone Therapy (BHT)

Please answer the next series of questions based on your beliefs on bioidentical hormone therapy (BHT) using the given scale:

15. Beliefs on BHT efficacy compared to non-bioidentical hormones

	Strongly Disagree	Disagree	Agree	Strongly Agree	Do not know
I believe BHT is as effective for the treatment of vasomotor symptoms associated with menopause as compared to non-bioidentical hormones.	○	○	○	○	○
I believe BHT is more effective for the treatment of vasomotor symptoms associated with menopause as compared to non-bioidentical hormones.	○	○	○	○	○
I believe BHT is as effective for the prevention of osteoporotic fractures as compared to non-bioidentical hormones.	○	○	○	○	○
I believe BHT is more effective for the prevention of osteoporotic fractures as compared to non-bioidentical hormones.	○	○	○	○	○

16. Beliefs on BHT risks compared to non-bioidentical hormones

	Strongly Disagree	Disagree	Agree	Strongly Agree	Do not know
I believe BHT has the same risk of cardiovascular disease (i.e. heart attacks, stroke) as compared to non-bioidentical hormones.	○	○	○	○	○
I believe BHT has less risk of cardiovascular disease (i.e. heart attacks, stroke) as compared to non-bioidentical hormones.	○	○	○	○	○
I believe BHT has the same risk of blood clots as compared to non-bioidentical hormones.	○	○	○	○	○
I believe BHT has less risk of blood clots as compared to non-bioidentical hormones.	○	○	○	○	○
I believe BHT has the same risk of breast cancer as compared to non-bioidentical hormones.	○	○	○	○	○
I believe BHT has less risk of breast cancer as compared to non-bioidentical hormones.	○	○	○	○	○
I believe BHT has the same risk of side effects as compared to non-bioidentical hormones.	○	○	○	○	○
I believe BHT has less risk of side effects as compared to non-bioidentical hormones.	○	○	○	○	○

17. Beliefs on estriol efficacy and risks compared to other estrogens

	Strongly Disagree	Disagree	Agree	Strongly Agree	Do not know
I believe estriol is as effective for the treatment of vasomotor symptoms as compared to other estrogens.	○	○	○	○	○
I believe estriol is more effective for the treatment of vasomotor symptoms as compared to other estrogens.	○	○	○	○	○
I believe estriol has the same risks as compared to other estrogens.	○	○	○	○	○
I believe estriol has less risks compared to other estrogens.	○	○	○	○	○

18. Beliefs on natural progesterone compared to synthetic progestins

	Strongly Disagree	Disagree	Agree	Strongly Agree	Do not know
I believe natural progesterone has less side effects compared to synthetic progestins.	○	○	○	○	○
I believe natural progesterone is associated with less risk of cardiovascular adverse effects compared to synthetic progestins.	○	○	○	○	○
I believe natural progesterone is associated with less risk of breast cancer compared to synthetic progestins.	○	○	○	○	○

19. Beliefs on compounded progesterone cream

	Strongly Disagree	Disagree	Agree	Strongly Agree	Do not know
I believe compounded progesterone cream can be used for the relief of vasomotor symptoms.	○	○	○	○	○
I believe compounded progesterone cream can be used to reduce the risk of endometrial hyperplasia in women with a uterus who are receiving estrogen therapy.	○	○	○	○	○

20. Beliefs on BHT and saliva testing

	Strongly Disagree	Disagree	Agree	Strongly Agree	Do not know
I believe testing of salivary estrogen and progesterone levels is useful in assessing hormone status.	○	○	○	○	○
I believe testing of salivary hormone levels is useful in determining the initial dose of estrogen and progesterone.	○	○	○	○	○
I believe saliva testing of estrogen and progesterone hormone levels is useful in the dose titration of BHT.	○	○	○	○	○

Section 4: Learning needs and confidence levels

21. Please indicate the extent to which you agree or disagree with the following statements

	Strongly Disagree	Disagree	Agree	Strongly Agree	Do not Know
I have identified gaps in my general knowledge of BHT that need strengthening.	○	○	○	○	○
I feel confident recommending BHT to a patient.	○	○	○	○	○
I feel confident providing patient education on BHT.	○	○	○	○	○

22. Are there any areas in which you feel additional training about BHT would be beneficial? (check all that apply)

☐ Safety and efficacy of BHT
☐ Availability of commercial BHT products in Canada
☐ Patient education about BHT
☐ Compounding of BHT products
☐ Saliva testing
☐ Other _____

Section 5: Pharmacy Practice Experiences:

23. In our research, we are interested in your experiences with BHT. Do you have any experiences that will help us understand your role with providing BHT to patients?

If you are interested in receiving more information about BHT, please contact the investigators at the following email address: tsiyam@pharmacy.ualberta.ca

To enter a draw to win one of two 8 GB ipod touch, please answer the following skill- testing question and provide your name and email address in the given spaces.

(12X12)/9 = _____

Name: _____ Email Address: _____

Appendix B: A table highlighting constructs, measures of constructs, items' coding and Cronbach's alpha values

Construct	Question	Items	Coding	Coefficient alpha
Knowledge on BHT definition	12	1. BH are chemical substances that are identical in molecular Structure to human hormones[a]	1=false, 2=true	0.703
		2. BH are natural, meaning they are non-synthesized hormones	1=true, 2=false	
		3.BH are natural, meaning they are extracted unaltered from plant sources	1=true, 2=false	
Beliefs about BHT efficacy in vasomotor symptoms compared to non-bioidentical hormones	15[b]	1.BHT is as effective for the treatment of vasomotor symptoms	1 to 4, anchored "strongly disagree" and "strongly agree"	0.801
		2.BHT is more effective for the treatment of vasomotor symptoms[a]	4 to 1, anchored "strongly disagree" and "strongly agree"	
Beliefs about BHT efficacy in osteoporosis compared to non-bioidentical hormones	15[b]	3. BHT is as effective for the prevention of osteoporotic fractures	1 to 4, anchored "strongly disagree" and "strongly agree"	0.777
		4. BHT is more effective for the prevention of osteoporotic fractures[a]	4 to 1, anchored "strongly disagree" and "strongly agree"	
Beliefs about BHT risks compared to non-bioidentical hormones	16	1. BHT has the same risks of cardiovascular disease	1 to 4, anchored "strongly disagree" and "strongly agree"	0.956
		2. BHT has less risk of cardiovascular disease[a]	4 to 1, anchored "strongly disagree" and "strongly agree"	
		3. BHT has the same risk of blood clots	1 to 4, anchored "strongly disagree" and "strongly agree"	
		4. BHT has less risk of blood clots[a]	4 to 1, anchored "strongly disagree" and "strongly agree"	
		5. BHT has the same risk of breast cancer	1 to 4, anchored "strongly disagree" and "strongly agree"	
		6. BHT has less risk of breast cancer[a]	4 to 1, anchored "strongly disagree" and "strongly agree"	
		7. BHT has the same risk of side effects	1 to 4, anchored "strongly disagree" and "strongly agree"	
		8. BHT has less risk of side effects[a]	4 to 1, anchored "strongly disagree" and "strongly agree"	
Beliefs about estriol efficacy compared to other estrogens	17[b]	1. Estriol is as effective in vasomotor symptoms	1 to 4, anchored "strongly disagree" and "strongly agree"	0.839
		2. Estriol is more effective in vasomotor symptoms[a]	4 to 1, anchored "strongly disagree" and "strongly agree"	
Beliefs on estriol risks	17[b]	3. Estriol has the same risks	1 to 4, anchored "strongly disagree" and "strongly agree"	0.894
		4. Estriol has less risks[a]	4 to 1, anchored "strongly disagree" and "strongly agree"	
Beliefs about natural progesterone risks compared to synthetic progestins	18	1. Natural progesterone has less risk of side effects	1 to 4, anchored "strongly disagree" and "strongly agree"	0.891
		2. Natural progesterone has less risk of cardiovascular adverse effects	1 to 4, anchored "strongly disagree" and "strongly agree"	
		3. Natural progesterone has less risk of breast cancer	1 to 4, anchored "strongly disagree" and "strongly agree"	
Beliefs about saliva testing	20	1. Salivary estrogen and progesterone levels is useful in assessing hormone status	1 to 4, anchored "strongly disagree" and "strongly agree"	0.959
		2. Salivary hormone levels is useful in determining initial dose of estrogen and progesterone	1 to 4, anchored "strongly disagree" and "strongly agree"	
		3. Saliva testing is useful in dose titration BHT	1 to 4, anchored "strongly disagree" and "strongly agree"	
Confidence in BHT[c]	21	1. I feel confident recommending BHT	1 to 4, anchored "strongly disagree" and "strongly agree"	0.865
		2. I feel confident providing patient education on BHT	1 to 4, anchored "strongly disagree" and "strongly agree"	

[a]items with reversed coding

[b]respondents agreeing to both items of these questions, were excluded from the data set before measuring cronbach's alpha (coefficient alpha)

[c]Confidence in recommending and providing patient education on BHT

Appendix C: Quotes from qualitative analysis

Arising Themes	Quotes Highlighting Themes
Confusion with term "BHT"	
Confusion with definition	- I am under the impression that so long as the hormones are the same chemical structure as those that can be produced by the human body they are considered bioidentical (i.e. not synthetic). that being said, I am under the impression they are still produced chemically in a lab (not extracted without any changes) - Commercial products containing Estrace, Estrone and Prometrium are made synthetically but are the same chemical structure that the body produces, some confusion with the term by many people, not sure if compounded products give the same bioavailability or are as effective - I believe there is a confusion regarding the public's definition of bioidentical Hormone and my definition - I don't have a specific definition of BHT which makes it difficult to answer the questions. I have two definitions. Any HRT that is not produced by the body naturally, or those that are defined by TV commercials as those that are naturally occurring and prepared to mimic hormone activity - Only saw BHT used while working in a compounding pharmacy as a student; however I had no direct compounding experience with it and was relatively unfamiliar with it in comparison to NBHT. In practice, I have only seen synthetic hormones being used therefore I am not too familiar with the BHT - In my short time as a practicing pharmacist, I have heard of one pharmacy that compounds BHT products, but I do not fully understand what BHT is. I feel very uncomfortable discussing BHT as I do not know very much about it. I am unaware as to what commercially available BHT products there are. I feel my education was extremely lacking in this area and think it would be an excellent idea to expose students to the area of BHT. I want to learn more about BHT but don't know where to find reliable information regarding BHT - The only experience with BHT that I for certain know that I have encountered was during rotation in BC and in NB. I have yet to encounter BHT in Southern Alberta. I believe it to be a useful therapy and would like to have more information. I think it would be valuable for our pharmacy to compound these products - BH may come from plant or synthesized sources, I think question 12 is misleading. - The bioidentical hormone term is very misleading to practitioners and patients. It promotes these products as much safer and natural when they are really no different than commercial products

Misinformation about BHT	- Products generally don't exist for a good reason and women are being ripped-off by greedy pharmacists making out that they are something special compared to their colleagues - Many women are interested in BHT. They have been led to believe, by advertising and even the term "BIOIDENTICAL", that BHT is safer than commercial products. - Personally, I would like to see more research done regarding BHT. I think there is a lot of misinformation that is being given to patients - Patients are finding there is a large gap in knowledge and treatment for menopause and a lot of misinformation. BHT needs to be studied properly with properly. I believe it will be shown to be a valuable tool in treating hormone related problems - I'm not involved with them at all. The claims have not been tested and are often over-hyped and media driven rather than fact-based (i.e. Suzanne Sommers) - Some women swear by it but I can't help but wonder if there is some placebo effect due to misconceptions published in the general media
Confusion in contrasting evidence	- I have avoided participating in BHT as it is an unproven practice, the salivary testing is inappropriate and seems, in general, a dodgy practice that makes unproven claims and tarnishes the profession because of it - In the past year, I attended a presentation put on by the West Coast Women's Clinic for Hormone Health (located in Vancouver) that was very pro-BHT, yet the information was not delivered in an evidence-based way. I practice in family physician clinics that strive to be evidence-based. However, there is very little "evidence" on BHT as compared to standard hormone therapy as far as I know - Began compounding as a new PCCA member last year, attended a 2 day seminar on BHRT in Edmonton last month, Dr. Pamela Smith M.D. MPH and Dr. G. Gillson PhD. M.D. presented. These practitioners presented material which portrayed BHRT in a very positive light and warned of the potentially dangerous effects of non-BHRT. As well, saliva testing was presented as the only practical way to measure free, unbound hormone levels and aid in determining appropriate doses. There was no mention of "total lack of evidence" that is cited by Gynecologists and Obstetricians Society????? - There are so many different articles educational material out there and it's hard to believe what is correct and what is not! - I was taught in school that topical progesterone was not absorbed. So, if it isn't either my patients have a large placebo effect, or it really dose relieve vasomotor symptoms on its own!

Lack of knowledge and need for education	
	- As a pharmacist involved in counseling patients and their physicians on BHRT, and given that all hormone therapies represent complex; interdependent physiological relationships, there is always a need for improved knowledge and understanding, especially as we continue to learn more about the discipline, as new research results become available and as we gain better understanding of the complexities. I myself have benefited from lectures on various, specific aspects of BHRT with the understanding that the complex nature of the subject sometimes requires that you see or hear the information several times, from different lecturers until an understanding of the subject can be gained. Without this kind of learning, without this level of understanding, my title would be Pharmacy Technician and not Clinical Pharmacist - I have never had an opportunity to learn much about the differences between BHT and non-BHT (but understand the effects/risks/benefits of hormones in general). BHT was not in fashion at the time I graduated. Any suggestions on reputable sources for information on this? - Wow, I clearly don't know much of anything regarding BHT. Any patients I have now on BHT have been on it forever and never have any questions or concerns about it (unless we can't get it in on time). I will be hunting around now for some CE opportunities - I never encounter this in my practice and I see a big knowledge gap for me in this area - I only have 1 year experience working in a compounding pharmacy that specializes in BHT. I have identified some gaps in my knowledge base after completing the survey. I will be concentrating my learning activities to help improve my ability to counsel clients effectively - During my years of practice in pharmacy, my pharmacy practice never intertwine with BHT. My knowledge of BHT is very limited. Before any recommendations made to anyone, I would have to do some research on that topic - I work in a PCN and do not dispense. My referrals are mainly for hypertension, diabetes, and dyslipidemia. Therefore, my exposure to BHT is very limited. However, I do realize that many of my patients are older women and the potential to be asked questions on BHT or HRT in general is high. Therefore, this is an area that I definitely need to review and learn more about - I was employed in an independent pharmacy that compounded BHT however, although the technician and pharmacist/owner had taken the course on compounding the preps, the pharmacist did not take a corresponding therapeutics course so he could provide very little in service teaching or patient teaching. He also did not know how dose was determined and so as such, i was hesitant to jump in and promote the service of compounding these specialty compounds....would love the opportunity to learn more either from a continuing education course or journal articles - no, i still need more update to be able to conduct these info to the patients - I feel that I am able to learn about bioidentical hormone therapy; however, I would like to receive non-biased objective information. I need training on all aspects of bioidentical hormone therapy - Sorry, I work with Cancer patient and in my practice I never deal with BHT, but I would love to know more if it is possible

	- I do not see BHT in my practice, but do have a few patients men and women asking questions regarding efficacy, safety, how it compares to commercial products available, etc. Not knowing many of the answers, I typically refer these individuals to other health care professional that are trained specifically on BHT - Sorry I'm completely clueless in this area so future continuing education in this area would be fabulous! - Not sure, I have just started working in a compounding pharmacy, so any extra info would benefit me greatly! Thank you - I feel my education was extremely lacking in this area and think it would be an excellent idea to expose students to the area of BHT. I want to learn more about BHT but don't know where to find reliable information regarding BHT - I basically have little to no experience with BHT. I've had a few customers ask questions about it, but that is about it. This is an area that I would really like to have some more education in, but have no idea where to get it! - In my practice I am focused on diabetes and pain management. There is the odd case where hormone replacement products are being used and questions do arise. I generally forward those questions on to someone with more experience in that area if possible. It would be nice to know more about BHT to allow me to answer a few more questions!! I do dispense periodically in retail and find this area a bit overwhelming
Supportive of compounding BHT	
CBHT a holistic approach to menopause management	- I believe there is a possibility that bio-identical hormones can be compounded to be more effective if only because in my experience BH supplementation therapy entails a holistic approach to menopause treatment. That and the possibility that if compounding a BH preparation, hormone combinations can be prepared and thereby used in the therapeutic approach. BH therapy also usually includes a more complete assessment of those other factors that influence hormone function, as well as other health issues that may be part and parcel with menopause complaints
Mimics physiological delivery of sex hormones	- I don't believe compounded BHT to be any more or less effective but that it can be customized to the patient more easily than commercially available products and that it mimics the physiological delivery of sex hormones more closely - My apology, for appearing to be "paranoid" but I have be involved with BHRT for long enough to know that every attempt is made to discredit or to paint this therapy as not "science based", when in fact it is based on good science and in some ways, I liken it to a therapeutic approach that seeks to mimic normal human physiology and to correct the dysfunction that so often leads to menopause as we know it

Getting right balance causes less risks	- Getting the right balance of the BH, I believe can give you less side effects, and possibly less risks of CVD/clots. It is all about balance and finding what works for each patient. To me it makes sense that our bodies would respond better to something it makes naturally (BH) instead of a foreign substance - Since we are mimicking the normal human physiology, in theory the incidence of many cancers should be less. But I'll qualify that and say that if it is an estrogen sensitive cancer, then using estradiol will produce the same risks. Instead however, what is available is either a non-estrogen supplement (if that is appropriate) or an Estriol only supplementation, where there is evidence (and not new) that many cancers are associated with decreased levels of Estriol. Too early to say that Estriol is "the" treatment but certainly points to some very exciting possibilities especially since this fits within a clinical picture that indicates that either excess estradiol or insufficient estriol may at least increase the risk of certain hormone sensitive cancers. And going forward, may we can reduce the risk of some cancers by addressing these imbalances earlier on
Saliva testing-useful tool	- I consider myself very confident is assessing BHT for patients that choose this for of hormone therapy. I always get the patient to saliva test their levels (for those that can afford the testing) for proper dosing. I have been using saliva testing for the past 7 years and found it to be the most useful tool to use to monitor patient therapy - I am aware of BHT only because of my personal breast cancer journey. I know that I will not use anything but bioidentical hormones but until now I am not using any kind of HRT.I strongly believe that the saliva testing should be available to everyone - I believe saliva testing is useful for initial assessment of hormone levels but after they have started therapy I don't believe they are as accurate. - Although I am convinced that saliva testing is extremely useful for the initial diagnosis and dosing of estrogen, progesterone and/or testosterone, I don't believe it is useful if certain compounded preparations are being used such as transdermal preparations. This is simply due to the fact that there is too much risk of transdermal hormone contaminating the saliva sampling procedure - giving an elevated hormone value in error. - Saliva testing is best suited for a general assessment of hormonal levels. Dosage is initiated at a low dose and titrated based on response. - Saliva testing MUST be used in conjunction with SYMPTOMS. I would NEVER do a re-test to titrate doses as there is no evidence to support this practice. As with commercially available products (BH and non-BH, treatment with compounded BH and dose adjustments should be made based on symptoms - We use the saliva testing a lot to do our HRT consults. I find them very handy both in initial dosing and titration - I manage a compounding pharmacy in Southeastern Alberta which compounds on average, about 30 customized prescriptions per day. BHRT is about 75% of our specialty compounding practice. We also provide the option of saliva testing (via Rocky Mountain Analytical in Calgary) as a diagnostic tool for our patients.

Quality of CBHT varies	- Many courses have to be taken regarding the counseling and compounding of these products. It is quite a specialized practice in pharmacy. Different bases result in different efficacies as well as the way these delivery systems are measured and applied. There are different delivery systems that are available and trial and error is often used to find the optimal choice of product and delivery system for the patient along with follow up tests such as saliva and blood tests in addition to the desired outcome of the therapy - I have compounded these products prior to my current job due to patient demands for the medication; not because I necessarily "believe".... PCCA pharmacists think they have the "ownership" of compounding which we know is not true..... any pharmacist can compound but we know vehicles have as much to do with drug availability as anything else. I feel this area lacking much in FACT and relies on BELIEF instead..... Patient Belief affects significantly how a patient feels about any diagnosis and treatment..... and compound this with pharmacist belief and the information becomes even more skewed.....
Knowledge about BHT	
Received additional training	- I have extensive experience with BH , have taken additional courses thru PCCA and work in a compounding pharmacy where BH are compounded and dispensed daily. I've been involved with assessing patients for their need for hormone replacement and in providing suggestions to physicians for starting doses or just general info about compounding alternatives - As described I have been involved with bio-identical hormone therapies since 1997, when my first patient came to me and asked, "What do you think about this progesterone therapy?" That was the start of my adventure which continues today. Since my first formal weekend workshop in Seattle, led by Dr. Roby Mitchell MD to my most recent PCCA sponsored educational symposium in Edmonton with speakers such as Dr. Pamela Smith and Dr. George Gillson, I have worked hard to become educated on the subject - Began compounding as a new PCCA member last year, attended a 2 day seminar on BHRT in Edmonton last month, Dr. Pamela Smith M.D. MPH and Dr. G. Gillson PhD. M.D. presented. These practitioners presented material which portrayed BHRT in a very positive light and warned of the potentially dangerous effects of non-BHRT. As well , saliva testing was presented as the only practical way to measure free, unbound hormone levels and aid in determining appropriate doses - I manage a compounding pharmacy in Southeastern Alberta which compounds on average, about 30 customized prescriptions per day. BHRT is about 75% of our specialty compounding practice. We also provide the option of saliva testing (via Rocky Mountain Analytical in Calgary) as a diagnostic tool for our patients. I have attended a number of workshops and symposiums on BHRT as a member of PCCA and use my expertise in this area to assist physicians who may be uncertain of where to begin when it comes to prescribing compounded hormone products. I have found that compounding is a valued niche opportunity which has given me much professional satisfaction and provided many valuable and positive patient outcomes - BHT compounding done and patient education done at previous place of practice -BHT course taken in Calgary by PCCA/Wiler

Seek professional development	- Hormones are extremely complex and the interplay between them is even more complex. I have taken a few advanced classes, but have recently decided to start training to become a Certified Menopause Practitioner. I don't think anyone can know everything in one particular area - our knowledge is always increasing! - As a pharmacist involved in counseling patients and their physicians on BHRT, and given that all hormone therapies represent complex; interdependent physiological relationships, there is always a need for improved knowledge and understanding, especially as we continue to learn more about the discipline, as new research results become available and as we gain better understanding of the complexities. I myself have benefited from lectures on various, specific aspects of BHRT with the understanding that the complex nature of the subject sometimes requires that you see or hear the information several times, from different lecturers until an understanding of the subject can be gained. Without this kind of learning, without this level of understanding, my title would be Pharmacy Technician and not Clinical Pharmacist
GP's lack knowledge on BHT	- I once had an Rx written by a GP, but it only said bio-identical hormones and so I was not sure how to interpret. It was then obvious, after consulting with colleagues, that the GP had no idea how to properly write the prescription so as to indicate the correct amounts of each specific hormone etc. More education on appropriate prescriptions and how to collaborate with GP's would be good - Patients want these products based on their own research. Some come in knowing what they want and others are gathering info. Md's seem happy to prescribe but often have little knowledge of products and will prescribe based on patient requests or our suggestions - We offer consults to come up with what women should ask their doctors for. We probably dispense the most BHRT in our city and try to educate and counsel patients as much as possible. The doctors need to be better educated as they don't know what to prescribe and some are so closed minded it is frustrating - A doctor wrote a script for BHT. We are a pharmacy who usually does not compound these products. The doctor did not specify what base to use for compounding. He gave me a really hard time for even calling him about it. He also indicated that he did not know what base it gets compounded into. I called a few local compounding pharmacies to see what they use and NONE of them would give me any suggestions. I tried to do some online research as well and did not come up with much luck. We ended up having to give the RX back to our longtime customer to have it filled elsewhere. We wanted to compound it, but lack of information prevented us. It scares me that not even the physician knew what it composed of - I have attended a number of workshops and symposiums on BHRT as a member of PCCA and use my expertise in this area to assist physicians who may be uncertain of where to begin when it comes to prescribing compounded hormone products

Non-supportive of compounding BHT	
Money-making scheme	- I know that a lot of pharmacies compound BHT products and that it is big business for them. I would have to feel confident that it was actually more helpful to patients before I would consider compounding them - I do not believe that everyone receiving BHT products are receiving the same product. I think that some pharmacies are using this treatment as a "cash cow" without regard for the patient - I currently feel that compounding BHT and saliva testing only have the purpose of making money for the people doing these things. I don't see a place for them in addition to currently available pharmaceutical grade BHT and blood testing. If this is not true, then I need further education in this area - I counsel customers about the science of BHT: I clarify that bio-identical includes commercially available products such as estradiol or micronized progesterone, and that products advertised as BHT are usually just custom compounded hormones that are not worth the money - This area is being touted by a few who have studied it and are making a big run with and for the money in it. Compounding does not have the fee structures that are monitored and set out well enough yet. There are some who do a good job of it and some that are snake oil salesmen who can and might wreck what could turn out to be a good thing - I know that a lot of pharmacies compound BHT products and that it is big business for them. I would have to feel confident that it was actually more helpful to patients before I would consider compounding them. - I believe the whole issue of BHT is largely a scam by independent pharmacies to profit from susceptible people. The sooner the whole issue of pharmacists compounding is stopped the better, not just for these products. Products generally don't exist for a good reason and women are being ripped-off by greedy pharmacists making out that they are something special compared to their colleagues
Saliva testing-insufficient evidence and a way for marketing BHT	- I believe saliva testing is just one more way for practitioners to make money - My experience is that it costs a lot of money, there is little scientific evidence to support compounding BHT and doing saliva testing and that it is an area that seems to prey on women and men who are suffering from other health issues - Saliva testing is probably not as useful for dosage adjustments as why would you adjust the dose based on levels? Should be based on symptom control. - I am skeptical about saliva testing in general - It is my understanding that saliva testing is controversial and dosing should rather be based on symptoms. - Saliva testing is not based on any good scientific evidence, and should be outlawed in Canada. It is unethical to take money from people for such a test - Blood work to determine hormone levels is not reliable; saliva testing must be less reliable. Why use a compounded product (questionable bioavailabilities) when manufactured, Canada government tested products are available? - I don't know if I have seen any scientific evidence with respect to saliva testing or if it's just a gimmick to promote BHT - I believe the efficacy of saliva testing has not been confirmed

Quality of CBHT varies- lacks standardization and federal regulation	- I often wonder if these compounding druggists have ever considered the potential liability of these products that they are making themselves without quality control procedures in place - I would have to review a head-to-head randomized comparative study which would be hard to do as these BHTs are compounded by various pharmacies so variability would be a concern - Quality of compounds key issue...different standards compared to manufactured - I don't think here is any evidence available that shows that topical progesterone is good enough to off-set the risk of estrogen on the uterus as the doses are not standardized - I feel there should be more regulation and standardization in this area. I do not believe that everyone receiving BHT products are receiving the same product

Appendix D: Details of multivariate regression analyses

A). Multiple linear regression analysis:

1a). Univariate analysis of demographics and practice related characteristics and *beliefs about the efficacy of BHT in vasomotor symptoms*:

Variables	T statistic	P value	decision
Gender (male vs. female)	-0.536	0.592	out
Age (≥30yr vs. <30yrs)	-1.619	0.107	in
Years of practice (>10yrs vs. ≤10yrs)	-0.381	0.704	out
Pharmacy school of graduation (U of A vs. other)	0.684	0.495	out
Type of practice (community vs. other)	-1.470	0.143	in
practice hours (full-time vs. part-time)	1.158	0.248	out
practice settings (urban vs. rural)	0.590	0.556	out
BHT compounding practice (yes vs. no)	-0.029	0.977	out

1b). Multivariate analysis of significant variables:

Variables	T statistic	P value	decision
Age (≥30yr vs. <30yrs)	-1.760	0.080	out
Type of practice (community vs. other)	-1.625	0.106	out

Conclusion: In the multivariate analysis, all variables were not significantly associated with *beliefs about the efficacy of BHT in vasomotor symptoms*.

2a). Univariate analysis of demographics and practice related characteristics and *beliefs about BHT efficacy in preventing osteoporotic fractures*:

Variables	T statistic	P value	decision
Gender (male vs. female)	-0.347	0.729	out
Age (≥30yr vs. <30yrs)	-0.393	0.695	out
Years of practice (>10yrs vs. ≤10yrs)	-1.290	0.201	out
Pharmacy school of graduation (U of A vs. other)	0.716	0.475	out
Type of practice (community vs. other)	-0.608	0.544	out
practice hours (full-time vs. part-time)	1.279	0.202	out
practice settings (urban vs. rural)	-0.422	0.674	out
BHT compounding practice (yes vs. no)	-0.787	0.433	out

Conclusion: In the univariate analysis, all variables were not significantly associated with *beliefs about the efficacy of BHT in preventing osteoporotic fractures.*

3a). Univariate analysis of demographics and practice related characteristics and *beliefs about BHT risks*:

Variables	T statistic	P value	decision
Gender (male vs. female)	-0.963	0.336	out
Age (≥30yr vs. <30yrs)	-2.569	0.011	in
Years of practice (>10yrs vs. ≤10yrs)	-0.859	0.391	out
Pharmacy school of graduation (U of A vs. other)	-1.339	0.221	out
Type of practice (community vs. other)	-2.590	0.003	in
practice hours (full-time vs. part-time)	1.026	0.306	out
practice settings (urban vs. rural)	-0.658	0.511	out
BHT compounding practice (yes vs. no)	-6.92	<0.001	in

3b). Multivariate analysis of significant variables:

Variables	T statistic	P value	decision
Age (≥30yr vs. <30yrs)	-2.158	0.032	in
Type of practice (community vs. other)	-1.497	0.136	out
BHT compounding practice (yes vs. no)	-5.871	<0.001	in

3c). Checking for confounders:

Variable	Beta	Beta with type of practice	Delta beta (%)
Age (≥30yr vs. <30yrs)	-0.165	-0.184	10.32
BHT compounding practice (yes vs. no)	-0.553	-0.512	8.00

3d). Model after dropping "type of practice":

Variables	T statistic	P value	decision
Age (≥30yr vs. <30yrs)	-1.316	0.032	out
BHT compounding practice (yes vs. no)	-6.662	<0.001	in

Since after the removal of type of practice age was rendered insignificant it was not included in the final main effect model

3e). Final main effect model:

Variables	B coefficient (95% CI)	T statistic	P value
BHT compounding practice (yes vs. no)	-0.57(-0.74, -0.41)	-6.92	<0.001

Conclusion: In the multivariate analysis, BHT compounding practice is the only variable that was significantly associated with *beliefs about BHT risks.*

4a). Univariate analysis of demographics and practice related characteristics and *beliefs about estriol efficacy:*

Variables	T statistic	P value	decision
Gender (male vs. female)	-2.752	0.007	in
Age (≥30yr vs. <30yrs)	-1.568	0.201	out
Years of practice (>10yrs vs. ≤10yrs)	-1.112	0.267	out
Pharmacy school of graduation (U of A vs. other)	0.169	0.866	out
Type of practice (community vs. other)	-2.088	0.038	in
practice hours (full-time vs. part-time)	0.425	0.672	out
practice settings (urban vs. rural)	0.400	0.690	out
BHT compounding practice (yes vs. no)	-5.474	<0.001	in

4b). Multivariate analysis of significant variables:

Variables	T statistic	P value	decision
Gender (male vs. female)	-1.462	0.145	out
Type of practice (community vs. other)	-0.383	0.702	out
BHT compounding practice (yes vs. no)	-4.679	<0.001	in

4c). Checking for confounders:

Variable	Beta	Beta with gender	Beta with type of practice	Delta beta (%)
BHT compounding practice (yes vs. no)	-0.370	-0.342	-	8.19
BHT compounding practice (yes vs. no)	-0.370	-	-0.355	4.23

4d). Final main effect model:

Variables	B coefficient (95% CI)	T statistic	P value
BHT compounding practice (yes vs. no)	-0.37(-0.50, -0.24)	-5.47	<0.001

Conclusion: In the multivariate analysis, BHT compounding practice is the only variable that was significantly associated with *beliefs about estriol efficacy.*

5a). Univariate analysis of demographics and practice related characteristics and *beliefs about estriol risks*:

Variables	T statistic	P value	decision
Gender (male vs. female)	-1.758	0.080	in
Age (≥30yr vs. <30yrs)	-2.321	0.021	in
Years of practice (>10yrs vs. ≤10yrs)	-2.856	0.005	in
Pharmacy school of graduation (U of A vs. other)	-1.543	0.124	in
Type of practice (community vs. other)	-3.602	<0.001	in
practice hours (full-time vs. part-time)	1.075	0.283	out
practice settings (urban vs. rural)	-1.079	0.282	out
BHT compounding practice (yes vs. no)	7.074	<0.001	in

5b). Multivariate analysis of significant variables:

Variables	T statistic	P value	decision
Gender (male vs. female)	-0.539	0.590	out
Age (≥30yr vs. <30yrs)	-0.629	0.530	out
Years of practice (>10yrs vs. ≤10yrs)	-1.550	0.123	out
Pharmacy school of graduation (U of A vs. other)	-1.805	0.072	out
Type of practice (community vs. other)	-2.284	0.023	in
BHT compounding practice (yes vs. no)	-5.617	<0.001	in

5c). Checking for confounders:

Variable	Beta	Beta with gender	Beta with age	Beta with years of practice	Beta with pharmacy school of graduation	Delta beta (%)
Type of practice (community vs. other)	-0.140	0.128	-	-	-	9.37
BHT compounding practice (yes vs. no)	-0.590	-0.582	-	-	-	1.37
Type of practice (community vs. other)	-0.140	-	-0.155	-	-	9.67
BHT compounding practice (yes vs. no)	-0.590	-	-0.562	-	-	4.98
Type of practice (community vs. other)	-0.140	-	-	-0.170	-	17.60*
BHT compounding practice (yes vs. no)	-0.590	-	-	-0.546	-	8.05
Type of practice (community vs. other)	-0.140	-	-		-0.160	12.50
BHT compounding practice (yes vs. no)	-0.590	-	-		-0.575	2.60

*Years of practice is a confounder

5d). Final main effect model:

Variables	B coefficient (95% CI)	T statistic	P value
Years of practice (>10yrs vs. ≤10yrs)	-0.19 (-0.34, -0.05)	-2.55	0.012
Type of practice (community vs. other)	-0.17 (-0.33, -0.02)	-2.182	0.030
BHT compounding practice (yes vs. no)	-0.55 (-0.73, -0.36)	-5.78	<0.001

Conclusion: In the multivariate analysis, years of practice, type of practice, and BHT compounding practice were significantly associated with *beliefs about estriol risks.*

6a). Univariate analysis of demographics and practice related characteristics and *beliefs about the less risk of natural progesterone*:

Variables	T statistic	P value	decision
Gender (male vs. female)	2.221	0.027	in
Age (≥30yr vs. <30yrs)	2.010	0.046	in
Years of practice (>10yrs vs. ≤10yrs)	0.386	0.342	out
Pharmacy school of graduation (U of A vs. other)	0.734	0.463	out
Type of practice (community vs. other)	3.731	<0.001	in
practice hours (full-time vs. part-time)	-0.281	0.779	out
practice settings (urban vs. rural)	1.55	0.121	in
BHT compounding practice (yes vs. no)	7.105	<0.001	in

6b). Multivariate analysis of significant variables:

Variables	T statistic	P value	decision
Gender (male vs. female)	1.143	0.254	out
Age (≥30yr vs. <30yrs)	1.269	0.206	out
Type of practice (community vs. other)	1.646	0.101	out
practice settings (urban vs. rural)	2.097	0.037	in
BHT compounding practice (yes vs. no)	6.044	<0.001	in

6c). checking for confounders:

Variable	Beta	Beta with gender	Beta with age	Beta with type of practice	Delta beta (%)
practice settings (urban vs. rural)	0.197	0.209	-	-	5.74
BHT compounding practice (yes vs. no)	0.672	0.652	-	-	3.06
practice settings (urban vs. rural)	0.197		0.196	-	0.51
BHT compounding practice (yes vs. no)	0.672	-	0.657	-	2.283
practice settings (urban vs. rural)	0.197			0.184	7.06
BHT compounding practice (yes vs. no)	0.672			0.619	8.56

6d). Final main effect model:

Variables	B coefficient (95% CI)	T statistic	P value
practice settings (urban vs. rural)	0.20 (0.02, 0.38)	2.152	0.032
BHT compounding practice (yes vs. no)	0.67 (0.49, 0.85)	7.28	<0.001

Conclusion: In the multivariate analysis, practice settings and BHT compounding practice were significantly associated with *beliefs about the less risk of natural progesterone.*

7a). Univariate analysis of demographics and practice related characteristics and *beliefs about the efficacy of compounded progesterone cream in vasomotor symptoms*:

Variables	T statistic	P value	decision
Gender (male vs. female)	0.749	0.455	out
Age (≥30yr vs. <30yrs)	0.722	0.471	out
Years of practice (>10yrs vs. ≤10yrs)	1.921	0.056	in
Pharmacy school of graduation (U of A vs. other)	0.645	0.519	out
Type of practice (community vs. other)	-0.056	0.965	out
practice hours (full-time vs. part-time)	-0.865	0.388	out
practice settings (urban vs. rural)	1.910	0.057	in
BHT compounding practice (yes vs. no)	4.469	<0.001	in

7b). Multivariate analysis of significant variables:

Variables	T statistic	P value	decision
Years of practice (>10yrs vs. ≤10yrs)	1.502	0.134	out
practice settings (urban vs. rural)	2.151	0.032	in
BHT compounding practice (yes vs. no)	4.349	<0.001	in

7c). Checking for confounders:

Variable	Beta	Beta years of practice	Delta Beta
practice settings (urban vs. rural)	0.172	0.176	2.27
BHT compounding practice (yes vs. no)	0.382	0.366	4.37

7d). Final main effect model:

Variables	B coefficient (95% CI)	T statistic	P value
practice settings (urban vs. rural)	0.17 (0.01, 0.33)	2.107	0.032
BHT compounding practice (yes vs. no)	0.38 (0.22, 0.55)	4.556	<0.001

Conclusion: In the multivariate analysis, practice settings and BHT compounding practice were significantly associated with *beliefs about the efficacy of compounded progesterone cream in vasomotor symptoms.*

8a). Univariate analysis of demographics and practice related characteristics and *beliefs about the efficacy of compounded progesterone cream in preventing endometrial hyperplasia*:

Variables	T statistic	P value	decision
Gender (male vs. female)	2.010	0.045	in
Age (≥30yr vs. <30yrs)	0.966	0.335	out
Years of practice (>10yrs vs. ≤10yrs)	1.157	0.248	out
Pharmacy school of graduation (U of A vs. other)	-0.737	0.462	out
Type of practice (community vs. other)	2.627	0.009	in
practice hours (full-time vs. part-time)	-0.779	0.437	out
practice settings (urban vs. rural)	1.365	0.173	in
BHT compounding practice (yes vs. no)	3.420	0.001	in

8b). Multivariate analysis of significant variables:

Variables	T statistic	P value	decision
Gender (male vs. female)	1.710	0.088	out
Type of practice (community vs. other)	1.542	0.124	out
practice settings (urban vs. rural)	1.834	0.068	out
BHT compounding practice (yes vs. no)	2.763	0.006	in

8c). Checking for confounders:

Variable	Beta	Beta with gender	Beta with type of practice	Beta with practice settings	Delta beta (%)
BHT compounding practice (yes vs.no)	0.347	0.332	-	-	4.52
BHT compounding practice (yes vs. no)	0.347	-	0.291	-	19.2*
BHT compounding practice (yes vs. no)	0.347	-		0.357	2.80

*Type of practice is a confounder

8d). Final main effect model:

Variables	B coefficient (95% CI)	T statistic	P value
Type of practice (community vs. other)	0.15 (0.03, 0.32)	1.67	0.095
BHT compounding practice (yes vs. no)	0.29 (0.15, 0.55)	2.74	0.007

Conclusion: In the multivariate analysis, BHT compounding practice was significantly associated with *beliefs about the efficacy of compounded progesterone cream in preventing endometrial hyperplasia*. Type of practice was a confounder,

9a). Univariate analysis of demographics and practice related characteristics and *beliefs about saliva testing*:

Variables	T statistic	P value	decision
Gender (male vs. female)	0.771	0.442	out
Age (≥30yr vs. <30yrs)	2.414	0.017	in
Years of practice (>10yrs vs. ≤10yrs)	2.555	0.011	in
Pharmacy school of graduation (U of A vs. other)	0.497	0.619	out
Type of practice (community vs. other)	3.680	<0.001	in
practice hours (full-time vs. part-time)	-2.094	0.037	in
practice settings (urban vs. rural)	1.679	0.095	in
BHT compounding practice (yes vs. no)	5.008	<0.001	in

9b). Multivariate analysis of significant variables:

Variables	T statistic	P value	decision
Age (≥30yr vs. <30yrs)	0.599	0.550	out
Years of practice (>10yrs vs. ≤10yrs)	0.730	0.466	out
Type of practice (community vs. other)	2.884	0.004	in
practice hours (full-time vs. part-time)	-1.463	0.145	out
practice settings (urban vs. rural)	2.149	0.033	in
BHT compounding practice (yes vs. no)	3.525	0.001	in

9c). Checking for confounders:

Variable	Beta	Beta with age	Beta years of practice	Beta with practice hours	Delta beta (%)
Type of practice (community vs. other)	0.317	0.333	-	-	4.80
practice settings (urban vs. rural)	0.276	0.266	-	-	3.75
BHT compounding practice (yes vs. no)	0.552	0.500	-	-	10.40
Type of practice (community vs. other)	0.317	-	0.328	-	3.35
practice settings (urban vs. rural)	0.276	-	0.269	-	2.60
BHT compounding practice (yes vs. no)	0.552	-	0.499	-	10.62
Type of practice (community vs. other)	0.317	-	-	0.335	5.37
practice settings (urban vs. rural)	0.276	-	-	0.279	1.07
BHT compounding practice (yes vs. no)	0.552	-	-	0.518	6.56

9d). Final main effect model:

Variables	B coefficient (95% CI)	T statistic	P value
Type of practice (community vs. other)	0.32 (0.08, 0.55)	2.646	0.009
practice settings (urban vs. rural)	0.28 (0.03, 1.58)	2.183	0.030
BHT compounding practice (yes vs. no)	0.55 (0.29, 0.81)	4.229	<0.001

Conclusion: In the multivariate analysis, type of practice, practice settings and BHT compounding practice were significantly associated with *beliefs about saliva testing.*

10a). Univariate analysis of demographics and practice related characteristics and *beliefs about confidence level*:

Variables	T statistic	P value	decision
Gender (male vs. female)	2.012	0.036	in
Age (≥30yr vs. <30yrs)	0.588	0.557	out
Years of practice (>10yrs vs. ≤10yrs)	0.746	0.456	out
Pharmacy school of graduation (U of A vs. other)	1.049	0.295	out
Type of practice (community vs. other)	6.211	<0.001	in
practice hours (full-time vs. part-time)	0.852	0.395	out
practice settings (urban vs. rural)	-0.302	0.763	out
BHT compounding practice (yes vs. no)	11.431	<0.001	in

10b). Multivariate analysis of significant variables:

Variables	T statistic	P value	decision
Gender (male vs. female)	0.788	0.431	out
Type of practice (community vs. other)	3.334	0.001	in
BHT compounding practice (yes vs. no)	9.846	0.000	in

10c). Checking for confounders

Variable	Beta	Beta with gender	Delta beta (%)
Type of practice (community vs. other)	0.252	0.244	3.27
BHT compounding practice (yes vs. no)	0.959	0.955	0.41

10d). Final main effect model:

Variables	B coefficient (95% CI)	T statistic	P value
Type of practice (community vs. other)	0.26 (0.11, 0.25)	3.487	0.001
BHT compounding practice (yes vs. no)	0.96 (0.77, 1.15)	9.905	<0.001

Conclusion: In the multivariate analysis, type of practice and BHT compounding practice were significantly associated with *beliefs about confidence level*.

B). Multiple logistic regression analysis:

11a). Univariate analysis of demographics and practice related characteristics and *knowledge on the definition of BHT*:

Variables	Wald's statistic	P value	decision
Gender (male vs. female)	0.000	.997	out
Age (≥30yr vs. <30yrs)	2.899	0.089	in
Years of practice (>10yrs vs. ≤10yrs)	2.55	0.110	in
Pharmacy school of graduation (U of A vs. other)	0.098	0.754	out
Type of practice (community vs. other)	0.000	0.991	out
practice hours (full-time vs. part-time)	2.562	0.109	in
practice settings (urban vs. rural)	3.883	0.049	in
BHT compounding practice (yes vs. no)	15.457	0.000	in

11b). Multivariate analysis of significant variables:

Variables	Wald's statistic	P value	decision
Age (≥30yr vs. <30yrs)	0.757	0.384	out
Years of practice (>10yrs vs. ≤10yrs)	0.794	0.373	out
practice hours (full-time vs. part-time)	1.616	0.204	out
practice settings (urban vs. rural)	4.465	0.035	in
BHT compounding practice (yes vs. no)	18.455	<0.001	in

11c). Checking for confounders:

Variable	Beta	Beta with age	Beta years of practice	Beta with practice hours	Delta beta (%)
practice settings (urban vs. rural)	0.738	0.738	-	-	0.00
BHT compounding practice (yes vs. no)	1.152	1.201	-	-	4.08
practice settings (urban vs. rural)	0.738	-	0.726	-	1.65
BHT compounding practice (yes vs. no)	1.152	-	1.237	-	6.87
practice settings (urban vs. rural)	0.738	-	-	0.716	3.07
BHT compounding practice (yes vs. no)	1.152	-	-	1.188	3.03

11d). Final main effect model:

Variables	Odds ratio (95% CI)	Wald's statistic	P value
practice settings (urban vs. rural)	2.09(1.08, 4.04)	4.797	0.029
BHT compounding practice (yes vs. no)	3.17(1.81, 5.52)	16.454	<0.001

Conclusion: In the multivariate analysis, practice settings and BHT compounding practice were significantly associated with *knowledge on the definition of BHT*.