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Current Best Practices, Evidence, Safety, and Efficacy Regarding Hormone Therapy Use for Menopausal and Postmenopausal Women

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CURRENT BEST PRACTICES, EVIDENCE, SAFETY, AND EFFICACY REGARDING HORMONE THERAPY USE FOR MENOPAUSAL AND POSTMENOPAUSAL WOMEN

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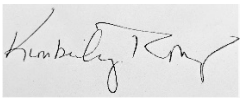
Project Advisor Signature: 

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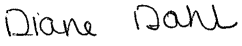
Dean/Chief Nursing Administrator Signature: 

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Abstract for Critical Review of the Literature

Background: Every woman will experience menopause, however each woman's experience is individual and has varying degrees of symptoms. As a woman ages estrogen production declines and eventually ceases. Hormone replacement therapy has been used for menopausal symptom management and for other conditions associated with declining estrogen. Information regarding hormone replacement therapy is conflicting and confusing. Evidence exists regarding safety and efficacy of hormone replacement therapy.

Purpose: The purpose of this critical review of the literature is to answer the practice questions of: What are the current best practices around hormone therapy use for menopausal and postmenopausal women? What is the current evidence regarding safety and efficacy of hormone therapy? The Theory of Symptom Self-Management provides the framework to partner with women to empower them to set individual health goals, to be able to make informed choices regarding the use of hormone replacement therapy, and self-manage their symptoms safely and effectively.

Results: Twenty-three articles were identified and evaluated for hormone replacement therapy evidence. The evidence is confusing and can be conflicting due to the many forms of hormone therapy, timing of treatment, length of treatment, and the misleading and unsupported endorsements. Hormone therapy can be used for treatment of menopausal symptoms for women as they transition into menopause. Hormone therapy has been shown to reduce cortical bone loss. However, in any case or any form, hormone therapy should be prescribed at the lowest dose for the shortest duration period possible. Use of hormone therapy increases a woman's risk for cardiovascular disease, thrombolytic events, cognitive decline, and breast cancer.

Conclusion: The review of the literature supports the evidence that hormone therapy can be used for short duration to treat symptoms of menopause. Every woman seeking information regarding

menopause and hormone replacement therapy should have a discussion with their provider care team to become informed about risk versus benefit of use and alternatives. Long term patient safety and a healthy life style should be emphasized.

Implications for Research and Practice: Providers and nurses need to be well informed about the different forms of hormone therapy and evidence surrounding the practice. Women's voices need to be heard and their symptoms affirmed. The Theory of Symptom Self-Management can be the framework for providers and nurses to partner with their patients and empower them to set healthy goals to safely manage their symptoms.

Keywords: Menopause, post-menopausal, hormone therapy, bioidentical hormone therapy, compounded bioidentical hormone therapy

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Chapter One: Introduction

The human body is an amazing and ever-changing dynamic system. As a woman ages, the body goes through life changes that seem to happen quietly over time. Hormones in the body are significant regulators during these changes. Declining estrogen and progesterone during menopause can create unpleasant and even life-altering symptoms and contribute to other disease formation. According to Stephenson, Neuenschwander, and Kurdowska (2013), "menopause impacts 25 million women worldwide each year, and by 2030 the World Health Organization estimates 1.2 billion women will be postmenopausal" (p. 74). "Menopause has been associated with symptoms of hot flashes, night sweats, dysphoric mood, sleep disturbance, and conditions of cardiovascular disease, depression, osteoporosis, osteoarthritis, dementia, and frailty" (p. 74). The World Health Organization (2017) reported that one in three postmenopausal women are impaired by osteoporosis, including a 40% lifetime risk of fractures from this devastating disease. Also associated with menopause is an increased risk of cardiovascular disease, affecting approximately one out of every three adult women. This increased risk of cardiovascular disease is predominately seen in women approximately ten years after menopause (American Heart Association, 2019). The increased risk of coronary heart disease can be partly explained by the phenomenon of the changing lipoprotein as estrogen declines (Formby & Schmidt, 2011).

Statement of Purpose

Replacement hormone therapy, that of estrogen alone or combined with progestin, has been used for years to help relieve menopausal symptoms (Ruiz & Daniels, 2014). Throughout this time, there has been conflicting advice regarding hormone use. The Women's Health Initiative study, which was initially started in 1993, released evidence in 2002 that suggested hormone replacement therapy increased a woman's risk of stroke and breast cancer (Fishman, Flatt, & Settersten, 2015; WHI, n.d.). Since then, other studies have been completed to assess the

effects of hormone use with women who have pursued traditional or other alternative hormone therapies. It is known that women are continuing to choose hormone therapy due to their experience with devastating symptoms during the menopause transition. In 2005, it was estimated that as many as two million women in the United States used compounded bioidentical hormones; in the year 2007, a court ordered hearing was done by the United States Senate to address the increase in compounded bioidentical use (Iftikhar, Shuster, Johnson, Jenkins, & Wahner-Roedler, 2011).

Over the last several years, knowledge about hormone replacement therapy has evolved. The practice questions to guide this critical review of the literature are: What are the current best practices around hormone therapy for menopausal and postmenopausal women? What is the current evidence regarding safety and efficacy of hormone therapy?

Hormone Therapy

There are several forms and types of hormone therapy available on the market today. Most traditional hormone therapy comes in a pill form and contains conjugated equine estrogen (Bhavnani & Stanczyk, 2012). Traditional hormone therapy is regulated and approved by the Food and Drug Administration. Alternative forms of hormone therapy which have been chemically modified from either plant or animal material are known as bioidentical (Fishman, et al., 2015). There are some forms of bioidentical hormone therapy that are regulated and approved by the Food and Drug Administration, for instance, estradiol and micronized progesterone (L'Hermite, 2017). There are also compounded forms of bioidentical hormones. Compounded forms are made by compounding pharmacies; these forms of hormones are not regulated or approved by the Food and Drug Administration.

Definitions

Identified topic-specific words and their definitions used throughout this literature review include the following:

Menopause: the transition or biological process when the ovaries decrease production of estrogen, which leads to the irreversible termination of menses (Schoor, 2015).

Postmenopause: a natural or surgical menopause where there has been at least one year since menstruation (Nii et al., 2015).

Osteoporosis: an overall bone disease; bone cells do not absorb within the bone structure which creates low bone density and leads to bone fragility and fractures. (Stephenson et al., 2013; Ran, Yu, Chen & Lin, 2017).

Dysphoric Moods: a state of mind such as depression, anxiety, and reduced self-esteem (Stephenson et al., 2013).

Transdermal: relating to administering medication topically, usually in the form of a dermal patch, gel, emulsion, or spray (Archer, Pickar, MacAllister, & Warren, 2012).

Bioidentical: a chemical composition that is the same as a human composition (Sood et al., 2013). Substances are usually extracted from plant sources and then chemically altered (Fishman et al., 2015).

Compounded Hormone Therapy: bioidentical hormone combinations that are prepared by a compounding pharmacist into buccal, sublingual, oral, transdermal, vaginal suppository, or subdermal pellet forms. A prescribed individualized combination of hormones (Fishman et al., 2015).

History of Hormone Replacement Therapy

Hormones were discovered in the early 20th century. During this time rejuvenation experiments and treatments were performed, using secretions extracted from testes and ovaries and then injected into men and women (Fishman et al., 2015). In the 1930s and 40s, the pharmaceutical companies promoted estrogen therapy to women. Over the next several decades, hormone therapy use grew. However, many studies emerged showing an increase in cancers associated with the use of estrogen replacement therapy. Due to this new evidence, the medical community recommended a limit to the time frame a woman would use replacement hormone therapy. Then in 1984, a professional medical organization invalidated any adverse claims by promoting hormone replacement therapy for osteoporosis (Fishman et al., 2015). The next several years brought acceptance to hormone therapy. In 1999 more than 85 million prescriptions for hormone replacement therapy were written (Fishman et al., 2015). Yet, as mentioned earlier, in 2002, a large scale study called the Women's Health Initiative (WHI) ended three years early due to the adverse outcomes and findings of increased risks of heart disease, stroke, and breast cancer (Fishman et al., 2015). Since then, there have been other observational studies performed using subsets of the initial participants from the original study. Some of the subset observational studies have suggested that hormone therapy provides coronary artery disease protection if initiated close to menopause (Mikkola, Savolainen-Peltonen, Venetkoski & Ylikorkala, 2017). Other studies demonstrate that age, pre-existing heart disease, time that the hormone therapy is started, and routes of hormone therapy were not taken into account in the WHI study, which can create differing outcomes (Nii et al., 2015).

Conflicting information exists regarding the risks and benefits of hormone therapy and thus has pushed many clinicians and patients to search for an alternative to the traditional

hormone therapy. Compounded bioidentical hormone replacement therapy is an alternative to the commercially available Food and Drug Administration approved bioidentical products. Bhavnani and Stanczyk (2012) suggest that, due to the conflicting information and distrust with traditional medicine, compounded hormones have become more popular.

Evidence Suggesting Need for Critical Review

A large study around the health effects of oral hormone replacement was stopped by the World Health Organization in 2002 because the health risks were determined to outweigh the health benefits for the women involved (World Health Organization, 2017). The study started enrollment in 1993 and was part of an attempt to raise awareness around health and focus on prevention of chronic diseases in postmenopausal women (National Heart, Lung, and Blood Institute, 2010; WHI, n.d.). The Women's Health Initiative involved 161,808 women aged 50-79 (National Heart, Lung, and Blood Institute, 2010). There were three main components to the initiative, one of which was a randomized control trial involving oral estrogen and progesterone. Since that time, there have been a multitude of studies which have found that the route of estrogen administration significantly impacts the therapy health risks associated with hormone replacement (Tremollieres et al., 2011). In addition, these studies have found that the type of progestin used in combination with estrogen can cause varying outcomes regarding the risk factors related to hormone replacement (Tremollieres et al., 2011). There continues to be confusion surrounding the use of hormone therapy.

Significance to Nursing

Menopause is a healthy and natural event in a woman's life. Some women have varying degrees of symptoms associated with menopause. Educating women on menopause and its symptoms can help women deal with the effects of these symptoms (Indra, 2016). Nurses are in a

position to bring knowledge to women in menopause, and advance awareness of the evidence about menopause and hormone use. Partnering with their patients, nurses can bring clarity to the issue and educate using current evidence. Providing positive support and increasing a woman's knowledge about normal body changes can improve both life expectancy and quality of life (Indra, 2016). Health care professionals must partner with their patients to establish trusting relationships, inform them of the current medical evidence, and create a plan of care for their individualized medical needs. Ultimately, any woman seeking information about menopause and replacement hormone therapy should discuss their personal medical history with their provider to establish and weigh their risks and benefits of hormone treatment.

Conceptual Framework

The Theory of Symptom Self-Management (TSSM) will provide a framework to the management of symptoms of menopause and increasing a woman's self-efficacy to safely manage menopause symptoms. This middle range theory includes characteristics of self-care and self-efficacy, recognizing a patient's behaviors and functional status to reach their set goals. The patient's perceived self-efficacy, characteristics, symptoms, and health behaviors are combined and used to develop performance outcomes. Most importantly is the collaboration of the health care provider or practitioner and the patient; together they partner to investigate interventions to help with empowerment and symptom self-management. Hoffman (2013) reports several studies in which the Theory of Symptom Self-Management was used successfully for patients with chronic and acute conditions and symptoms. "Self-management is a critical success factor for chronic illness management and the aim is to ensure that the patient is recognized as the source of control" (Hoffman, 2013, p 17).

How a patient perceives themselves and their symptoms is an essential component of the Theory of Symptom Self-Management. Developing an enhanced self-perspective using interventions that the patient can successfully perform is how the patient can be empowered. Also, offering observational experiences for them to see patients that are having similar health concerns with positive outcomes, and using verbal encouragement to help set goals is the groundwork for TSSM (Hoffman, 2013). The Theory of Symptom Self-Management incorporates specific patient characteristics, such as their physiological and psychological influencing factors, which is necessary when partnering with the patient to develop an individualized plan of care.

The Theory of Symptom Self-Management can be used to understand the perceived symptoms of menopause and how it affects the patient's health and self-image. Partnering with the patient to educate on symptom management, current evidence on hormone therapy, and healthy lifestyle changes is one of the first steps in the Theory of Symptom Self-Management model. Use of the Theory of Symptom Self-Management model with women experiencing or transitioning into menopause will help the women understand the changes they may be experiencing and will empower them to set healthy goals for a positive health outcome.

Summary

In this first chapter, the changes that occur with aging and the adverse effects of menopause have been presented. Topic specific definitions were included. Detailed information was presented on the history of hormones, and how over the years, conflicting information has brought confusion and distrust with traditional hormone therapy. The purpose of this critical review of the literature is to investigate current best practices, safety and efficacy, and compare how these relate to a woman's knowledge and beliefs of hormone therapy. The significance for

nursing has been identified along with the Theory of Symptom Self-Management for the application of enhancing self-efficacy for optimized patient outcomes.

Chapter Two: Methods

The purpose of this chapter is to describe the search strategies used to identify relevant research studies for this critical review of the literature. The topic of hormone therapy for overall risks, benefits, and use for menopausal and postmenopausal women will be further investigated. The literature was also reviewed for present-day knowledge, evidence, and beliefs associated with hormone therapy. The search strategies included specific inclusion and exclusion criteria, as well as the process and guidelines used to evaluate each study.

Search Strategies

Journal articles were gathered from the National Center for Biotechnology Information (NCBI), National Institute of Health, Pub Med, and Cumulative Index to Nursing and Allied Health Literature (CINAHL). Several inquiries were performed using the search terms of postmenopausal and menopausal women, hormones, hormone therapy, transdermal, bioidentical, and compounded hormone therapy. Particular attention was given to studies and articles that were five years old or less, and this was advanced to include relevant studies that were older to expand the literature findings. The years of publication for the studies and articles in this literature review range from 2011 to 2017.

Criteria for Evaluating the Studies

Altogether 23 articles were evaluated using The Johns Hopkins Nursing Evidence-Based Practice Model and Guidelines (Dearholt & Dang, 2012). The Johns Hopkins model identifies levels of evidence used to analyze, synthesize, and interpret literature (Dearholt & Dang, 2012). Each level is categorized based on the level of evidence. A randomized control trial is the highest level, which is level I. Level I can also include systematic reviews of more than one randomized control trial. Level II includes quasi-experimental studies which include manipulation of the independent variable and some degree of control or randomization (Dearholt & Dang, 2012).

Level II can also include systematic reviews of a combination of RCTs and quasi-experimental studies. Level III includes non-experimental quantitative studies and qualitative studies which explore a subject through interviews, surveys, or focus groups (Dearholt & Dang, 2012). Level IV is considered non-research and includes recommendation statements from national experts that are based on scientific evidence. Lastly, literature included in the level V category includes opinions from individuals or professional organizations that are considered the experts of the subject matter (Dearholt & Dang, 2012).

The standardized rating system also includes a quality rating. The highest quality is rated A is given to studies with sample sizes sufficient for the design, congruous evidence, and clear recommendations. A quality rating of B is considered good quality. Good quality consists of appropriately uniform results, sample size adequate for the design of the study and some control noted within the study, and there may have been some control noted within the study (Dearholt & Dang, 2012). The lowest quality is C, which allows for variable sample size, evidence, and recommendations (Dearholt & Dang, 2012).

Inclusion and Exclusion Criteria

Articles that met the inclusion criteria reported studies with menopausal and postmenopausal women who had used or were currently using hormone therapy. Articles were included which provided chemical and pharmaceutical information on compounded and or bioidentical hormones. Also, articles were included to show the current use of and trends in hormone therapy (HT). Due to non-Food and Drug Administration approved compounded bioidentical hormone therapy, there is no way of knowing exactly how many women are actively using compounded bioidentical hormone therapy, therefore an international study with comparative data was included (Velentzis et al., 2016). Exclusion criteria included studies

conducted earlier than the year 2011, studies with inconsistent results or recommendations, and articles not pertaining to menopause and postmenopausal women. Therefore, articles that incorporated men were excluded from this critical review of the literature. Ongoing extension studies from two well known earlier studies, which were the Women's Health Initiative (WHI) and Kronos Early Estrogen Prevention Study (KEEPS), were included; this provided critical evidence that pertained to but was not limited to, current use and beliefs of hormone therapy. The original WHI and KEEPS studies provided principle evidence on hormone use in menopausal and postmenopausal women. These studies are seminal studies which contain critical data for the basis of future studies. However, due to the age of these studies, the older, original studies were not included in this literature review.

A Summary of Study Type and Quality

A total of 23 articles were identified as meeting the criteria for selection for this literature review. Each article is organized into a matrix (see Appendix) that summarizes the content. There are ten articles that have level I evidence, five of which are high quality (Espeland et al., 2017; Farr, Khosla, Miyabara, Miller, & Kearns, 2013; Gleason et al., 2015; Ran et al., 2017; Whedon, KizhakkeVeettil, Rugo, & Kieffer, 2017). Out of this level I, high quality evidence, two of the five articles are reports of randomized control trials which were a continuation of the original KEEPS study, rated as high quality due to the sample size, consistent results, and adequate control (Espeland et al., 2017; Farr et al., 2013). Four articles that provide level I evidence report studies that are good quality with reasonably consistent results and a fairly definite conclusion (Allen, McCubbin, Loveless, & Helfer, 2014; Kocoska-Maras et al., 2013; Nii et al., 2015; Sood et al., 2013). One of the articles that provide level I evidence was rated low

quality due to the small sample size and missing specimens during the testing period (Pingel et al., 2012).

Articles providing level II evidence included five quasi-experimental studies that were all good quality due to the randomization of study assignment, consistent results, and reasonable recommendations (Carmona-Sanchez et al., 2013; Formby & Schmidt, 2011; Połac, Borowiecka, Wilamowska & Nowak, 2013; Ruiz & Daniels, 2014; Stephenson et al., 2013). Level III evidence included five qualitative studies all of which were good to high quality, and one correlational study of good quality. Of the five qualitative studies two were rated as high quality due to large sample size, some randomization into groups, and validated survey materials (Pinkerton & Santoro, 2015; Velentzis et al., 2016). Four of the studies that provided level III evidence have a quality rating of B for sufficient sample size, some rater bias, and use of a non-validated survey tool prior to the start of the study (Canonico et al., 2012; Fishman et al., 2015; Iftikhar et al., 2011; Thompson, Ritenbaugh & Nichter, 2017).

A position statement from the US Preventative Services Task Force was included and is level IV high quality evidence (USPSTF, 2017). Lastly, included was one expert opinion article from The American College of Obstetricians and Gynecologists that is level V high quality evidence due to expertise of subject matter and definitive conclusions (The American College of Obstetricians and Gynecologist, 2012).

Summary

This literature review was a systematic investigation into research studies to gain knowledge about issues that women face during menopause and post-menopause. The review of the literature investigated best practices around HT for menopausal and postmenopausal women, and determined current evidence regarding safety and efficacy of HT. Each study was evaluated

based on the Johns Hopkins Research Evidence Appraisal Tool for the level of strength and quality (Dearholt & Dang, 2012). The studies were categorized and summarized using the Evidence Synthesis Tool (Dearholt & Dang, 2012).

Chapter Three: Literature Review and Analysis

Chapter three provides a comprehensive review and analysis of each study and article for significant findings. A total of 23 studies and articles were gathered for information in an attempt to answer the project practice questions: What are the current best practices around hormone therapy use for menopausal and postmenopausal women? What is the current evidence regarding safety and efficacy of hormone therapy? Significant findings are categorized into themes that emerged within the literature. The strengths and weaknesses of the literature analyzed are brought forward and discussed. Finally, each study and article is outlined within the matrix (see Appendix).

Synthesis of Major Findings

Within the critical review of the literature, different forms of hormone replacement therapy were investigated for the varying menopausal symptoms and common chronic medical conditions that can appear with age. The United States Task Force recognizes that chronic conditions or the risk of coronary heart disease, dementia, fractures, and breast cancer can all increase with age. However, the percentage of these conditions that can be attributed to declining estrogen is not known (USPSTF, 2017). The articles under review have differences noted in traditional versus bioidentical and compounded bioidentical hormone therapy, as well as timing and duration of use. Included in this literature analysis are qualitative studies that explore the reasons women seek hormone therapy.

Menopause symptoms

Cognitive function. Menopausal symptoms due to declining estrogen, such as depression, anxiety, hot flashes, and sleep disturbances can be devastating. Four of the level I randomized controlled trials investigated the effect of hormone therapy (HT) on cognitive function and mood

effects. In a study with 693 menopausal and postmenopausal women, Gleason et al. (2015) reported oral menopausal hormone therapy does not improve cognition, although significant improvement in anxiety and depression was noted. Both oral and transdermal routes of hormone therapy were investigated and it was found that transdermal routes did not show benefits (Gleason et al., 2015). To expand on this finding, Espeland et al. (2017) examined data from the Women's Health Initiative Memory Study (WHIMS) of Younger Women, and the Women's Health Initiative (WHI) randomized controlled clinical trials, which included older women. Espeland et al. (2017) explained findings from both of these studies. Hormone therapy started at menopause, with younger women, had no cognitive benefit or disadvantage. However, hormone therapy initiated in older women resulted in a small reduction in several cognitive functions. These changes in cognitive function were reported to last several years after the HT was stopped (Espeland et al., 2017). Statistically significant decline in global cognitive functioning, verbal knowledge, and verbal fluency was seen in women aged 65-79 years old that were assigned to hormone therapy (Espeland et al., 2017). Over time the brain accommodates to the loss of estrogen and uses other energy sources such as ketones and fatty acids. When estrogen is brought back into the system, there is a disruption in this natural transition and cognitive function can be impaired (Espeland et al., 2017).

Similar findings were reported in a study conducted on 200 women randomly assigned to estrogen, testosterone, or placebo treatment for one month. Kocoska-Maras et al. (2013) declared that hormone therapy did not increase fluency, spatial memory, or verbal ability within this study group. The author acknowledged that other studies have shown testosterone induced positive, although not significant, trends on spatial memory (Kocoska-Maras et al., 2013). In a systematic review of 10 randomized control trials investigating bioidentical estrogen for the use of

menopausal depressive symptoms in 1,028 women, Whedon et al. (2017) found no significant improvement. The authors acknowledged their findings were consistent with the WHI study. In all ten studies included in the systematic review, only one type of bioidentical hormone was investigated. The author recommended that there be more studies with different types and combinations of bioidentical and nonbioidentical HT (Whedon et al., 2017).

Menopausal symptoms. In opposition to the above finding, and to again point out that there is conflicting evidence available to women seeking advice on alleviating menopausal symptoms, several of the level II quasi-experimental studies showed hormone therapy improved menopausal symptoms. Stephenson et al. (2013) showed statistically significant decreases in depression and dysphoric moods for women who used transdermal compounded bioidentical hormone therapy. The authors of this study support the use of transdermal compounded bioidentical hormone therapy, with recommendations for transdermal compounded bioidentical hormone therapy to be considered safe for menopausal symptoms. Another two level II studies investigated the effectiveness of bioidentical hormone therapy for menopausal symptoms. One of the studies compared transdermal and sublingual forms of bioidentical hormone therapy. Formby and Schmidt (2011) reported after three and six months of bioidentical hormone therapy, saliva levels of estrogen and progesterone significantly increased along with a significant fall in menopausal symptoms as reported by the Kupperman index. The Kupperman index is a well known, validated survey tool, which evaluates eleven of the most prevalent menopausal symptoms. Formby and Schmidt (2011) concluded that bioidentical hormone therapy at cyclical cycles, demonstrated positive results of both physiological and clinical outcomes. Supporting this conclusion, Ruiz and Daniels (2014) found participants receiving sublingual hormone replacement had the most significant reduction in menopausal symptoms. Furthermore,

sublingual hormone therapy had faster and more significantly improved outcomes versus transdermal treatment (Ruiz & Daniels, 2014). However, over more extended periods of use, small improvements in mood and night sweats were seen with transdermal therapy (Ruiz & Daniels, 2014).

Body system changes

***Cardiovascular and homeostasis effects*.** Of the level II evidence, the main focus of four of the studies was cardiovascular effects, which included inflammation, cholesterol, and clotting factor results in women who were currently or had ever used hormone therapy. Stephenson et al. (2013) examined not only the long-term effects of transdermal application of compounded bioidentical hormone therapy on depression, but also cardiovascular markers, which included inflammatory and immune signaling factors in menopausal and postmenopausal women. The study was conducted over three years, which in this context implies the definition of long-term. Within this study, statistically significant changes in inflammatory and immune signaling factors were seen with transdermal hormone therapy (Stephenson et al., 2013). Also, along with the other benefits of compounded bioidentical hormone therapy shown in this study, fasting glucose and triglycerides decreased significantly. Contradictory to the prior study, Canonico et al. (2012) found that higher levels of estrogen are associated with higher levels of fibrinogen, which can promote inflammation in postmenopausal women.

Połac et al. (2013) investigated oral versus transdermal hormone therapy, and reported after six months that fibrinogen levels were higher, and thrombin activity was statistically higher in the oral hormone therapy group. Although both transdermal and oral hormone therapy groups showed an increase in fibrinogen levels, the oral hormone therapy group had the most significant increase. The author's recommendations around hormone therapy for menopausal treatment are

to choose the safest product with the lowest known changes in coagulation and fibrinogen effects. Also, more studies are needed to evaluate the efficacy and safety of hormone therapy (Polac et al., 2013). These findings are an essential point to review because of the many different forms of hormones on the market, and the unique physiologic make-up of each woman. An evaluative pharmacy study on compounded bioidentical hormones found skin physiology, blood flow, and hormone metabolism can all affect hormone serum levels (Sood et al., 2013).

These findings can also contribute to more confusion for women when trying to understand the evidence that exists on hormone products. Nii et al. (2015) investigated the hepatic effects of three different types and routes of estrogen administration on cholesterol production. The authors of this study found different hepatic effects with different routes and doses of estrogen (Nii et al., 2015). These different effects may be associated with the risk of cardiovascular disease because of the impact on low density lipoprotein (LDL), high density lipoprotein (HDL), and free radical production (Nii et al., 2015). Allen et al. (2014) found that during stress there was a significant increase in systolic blood pressure across all study groups. However, the most significant increase was in the hormone therapy/placebo group. The smallest increase was seen in the hormone therapy/naltrexone group. This study attempted to explain the endogenous opioids relationship and the effects of estrogen during stress. Allen et al. (2014) concluded that this relationship correlates with and elevates the coronary heart disease risk when taking hormone therapy.

Bone and collagen turnover. Farr et al. (2013), in a KEEPS trial sub-study of seventy-six menopausal women, established that cortical bone is responsive to estrogen, and estrogen replacement therapy prevents the loss of cortical bone. Within this study, transdermal and oral conjugated estrogen were trialed. The authors recommended that more studies were needed to

investigate the site and route-specific forms of estrogen (Farr et al., 2013). Also, Ran et al. (2017) in a five-year study of 120 women in menopausal transition found a significant increase in bone mass density in oral hormone replacement groups in conjunction with a daily exercise routine. The increase in bone density was seen in the first two years, then it continued to decrease. However, at the end of the fifth year, bone mass density remained higher than before treatment for the hormone replacement groups (Ran et al., 2017). Similar findings were described in a study by Pingel et al. (2012), which investigated collagen stimulation effects in women on replacement hormone therapy and exercise. It was reported at day five of treatments with transdermal hormone therapy and exercise that serum collagen markers were significantly higher. This increase in the collagen marker effect was reported to expand with increased duration of use of the transdermal hormone therapy (Ran et al., 2017). A recommendation statement from USPSTF (2017) addressed hormone therapy for the prevention of postmenopausal osteoporosis. Individual characteristics and specific risk factors for chronic conditions such as osteoporosis should be advised using harm versus benefit ratio. Also, hormone therapy should be prescribed at the lowest dose for the shortest duration (USPSTF, 2017).

Breast density and risk of breast cancer. Due to several of the articles referencing an increased risk of breast cancer when using hormone therapy, a study assessing the effects of long term hormone therapy on breast density was included. Carmona-Sanchez et al. (2013) asserted increased breast density could hide or make it difficult to detect a small mass and is associated with the increased risk of breast cancer. This study was conducted over five years, which in this instance is considered long-term. The study included 165 postmenopausal women receiving transdermal hormone therapy. All study participants received estrogen, which was beta-estradiol

at the same strength. The study participants with a uterus also received progesterone, divided between two different forms and strengths. Mammogram x-ray reports were done at baseline, one year, and five years. Although all women in this study received transdermal hormone therapy, three different combinations of transdermal hormone therapy were studied. At one and five years, all women in the study showed increased breast density. Women on combined hormone therapy showed the most significant increase in breast density as compared to women on estrogen therapy alone (Carmona-Sanchez et al., 2013). Women on a cyclic combined hormone therapy had the most significant increase in breast density at five years (Carmona-Sanchez et al., 2013). These findings are consistent with the USPSTF recommendation statement. Combined estrogen and progesterone was evaluated with a moderate harm risk for invasive breast cancer (USPSTF, 2017).

The use of bioidentical hormones

Movement toward CBHT. The shift towards compounded bioidentical hormone therapy (CBHT) is thought to be an effort to seek improved health, well-being, and control due to choice (Iftikhar et al., 2011). There are regulated Food and Drug Administration approved bioidentical forms of hormone therapy, but women and some physicians are drawn to the compounded bioidentical hormone therapy. Thompson et al. (2017) explain a push-pull phenomenon in women who are seeking hormone therapy for menopausal symptoms. Push meant women are pushed to compounded bioidentical hormone therapy because of frustration with the conflicting hormone therapy information, lack of trust with the medical community, and media accounts of cancer from traditional hormone therapy. Pull meant women are pulled to use compounded bioidentical hormone therapy due to the perception it is safer, the belief it is effective in controlling their symptoms, and longing for individualized treatment (Thompson et al., 2017).

These findings are similar to the results of a study by Fishman et al. (2015), which investigated clinicians' practice and views of aging and medicine, and patient perceptions and experience with anti-aging therapies. Women are drawn to compounded bioidentical hormone therapy and the clinicians who prescribe it because they felt like the clinicians listened to them and validated their concerns and menopausal symptoms (Fishman et al., 2015). The clinicians that prescribed compounded bioidentical hormone therapy regarded themselves as good listeners, and felt they have the ability to care holistically (Fishman et al., 2015).

Safety and purity of CBHT. Compounded bioidentical hormones have not been adequately studied. Also, there is not the same Food and Drug Administration approval or regulation for these types of hormone therapy products (Sood et al., 2013). This literature review includes five level III qualitative studies that all analyze what percentage of women use compounded bioidentical hormone therapy, why compounded bioidentical hormone therapy is chosen, and what the current beliefs are around compounded bioidentical hormone therapy and traditional hormone therapy. This information is essential due to the fact that compounded bioidentical hormone therapy is not FDA regulated because it is not a standardized pharmaceutical product. Conventional medical and science's general opinion is that compounded bioidentical hormone therapy has the same risk and benefits of standard hormones (Thompson et al., 2017). Without the mandated regulations of the Food and Drug Administration, there is concern about the quality and safety of compounded bioidentical hormone therapy. Also, dose ranges are not controlled; this leaves compounded bioidentical hormone therapy users vulnerable to substandard dosing, which highlights other concerns around cancer (Thompson et al., 2017). Advertising for compounded bioidentical hormone therapy acclaims it to be natural, therefore there is an underlying misrepresented claim of safety (Iftikhar et al., 2011). An article that

provides level V evidence included in this review is an expert opinion article from The American College of Obstetricians and Gynecologists (2012). Within this article, conclusions and recommendations are outlined about compounded bioidentical hormone therapy use. Evidence is lacking to support claims of compounded bioidentical hormone therapy use. Also, efficacy and safety based on salivary, serum, or urine testing are deficient (The American College of Obstetricians and Gynecologist, 2012). There is an increased risk associated with compounded bioidentical hormone therapy in regard to product strength and sterility. The packaging of the compounded bioidentical hormone therapy product lacks safety data that should be included (The American College of Obstetricians and Gynecologist, 2012).

Numbers and knowledge of hormone therapy. In an attempt to approximate numbers of compounded bioidentical hormone therapy users, Velentzis et al. (2016) surveyed women of the Medicare enrollment database from Australia's universal health plan. It was found roughly between 2% and 15% of women who chose hormone therapy also chose bioidentical hormone therapy. This information is critical when looking at the understanding and knowledge about hormone therapy of women who chose compounded bioidentical hormone therapy. Pinkerton and Santoro (2015) estimated that between one and 2.5 million United States women use compounded bioidentical hormone therapy, even though not all understand or are aware of the difference between Food and Drug Administration approved or compounded hormone therapy. Pinkerton and Santoro (2015) identified that of the women who choose compounded bioidentical hormone therapy, between 14% and 27%, did not know if their current hormone therapy was compounded bioidentical hormone therapy, and 76% did not answer questions about compounded bioidentical hormone therapy correctly. Providers should be educating and advising patients on both the risks and the benefits of hormone therapy, the information should be

provided on the differences between Food and Drug Administration approved and compounded bioidentical hormone therapy, and caution should be taken when prescribing compounded bioidentical hormone therapy (The American College of Obstetricians and Gynecologist, 2012).

Strengths of the Most Salient Studies

All articles and studies have been evaluated for level and quality of evidence, based on the Johns Hopkins Guidelines (Dearholt & Dang, 2012). Included in this critical review of the literature are several level I, II, and III research studies with high and good quality ratings in an attempt to answer the practice questions posed for this project. Espeland et al.'s (2017) systematic review with meta analysis contains data derived over many years from 2008–2015, as well as evidence which was found to be consistent with other studies. The second salient study addressed the different effects between oral versus transdermal hormones. Gleason et al. (2015) investigated data from over 600 women. The women were randomized into three different groups, which were oral hormone therapy, transdermal hormone therapy, and a controlled method with a placebo. This investigation was conducted over four years and produced data with consistent results, provided uniform recommendations, used good references, and had adequate comparisons to other large studies. A third salient study identified the usage and the knowledge of the various hormone therapies within the United States. Pinkerton and Santoro (2015) used a cross sectional internet survey method to interview women who had either previously or currently used hormone therapy. Using the cross sectional method, with large numbers of participants, enabled the results to be compared for consistency.

Weaknesses of the most Salient Studies

Pingel et al.'s (2012) randomized control trial reported missing specimens during the testing period, which could have had an effect on the overall study outcome. Prior co-morbities

were reported within the study, however, the relationship of health related co-morbities and the use of hormone therapy cannot be ruled out or entirely explained when reporting estrogen and fibrinogen levels (Canonico et al., 2012). Inconsistent study results with over generalized recommendations were given from a quasi-experimental study done to evaluate the efficacy of bioidentical transdermal hormones that was conducted on a small sample size of 29 women (Formby & Schmidt, 2011). In one of the qualitative studies, a survey tool was not validated prior to its use in the study (Iftikhar et al., 2011). Lastly, several of the studies reported that the study participants were a generalization of the greater population, when it did not appear that this was true (Gleason et al., 2015; Pinkerton & Santoro, 2015; Ruiz & Daniels, 2014; Thompson, et al., 2017; Velentzis et al., 2016).

Summary

Within this chapter, 23 articles and studies were reviewed for information about risk and benefits, current knowledge, beliefs, and practices regarding hormone therapy and compounded bioidentical hormone therapy use. The significant findings were detailed and categorized into evidence levels according to the Johns Hopkins Nursing Evidence-Based Practice: Model and Guidelines (Dearholt & Dang, 2012). Strengths and weaknesses were outlined and allocated. Lastly, each article was organized into a matrix (see Appendix) that summarized the content.

Chapter Four: Discussion, Implications, and Conclusions

The focus of this literature review was to search for an understanding around menopause, the use of hormone therapy for menopausal symptoms, and possible prevention of chronic conditions that appear as a woman ages. This literature review also revealed current best practices for hormone replacement therapy, and evidence about safety and efficacy of bioidentical, compounded bioidentical, and traditional hormone therapy. The practice questions to guide this critical review of the literature were: What are the current best practices around hormone therapy use for menopausal and postmenopausal women? What is the current evidence regarding safety and efficacy of hormone therapy? In this chapter current trends and gaps in the literature are discussed, in addition to recommendations for further research. Implications for nursing practice to help educate and partner with patients and the use of the Theory of Symptom Self-Management are applied.

Synthesis of the Literature

Over the last several decades, knowledge about hormone replacement therapy has evolved. Information from ongoing seminal research studies has revealed details about traditional hormone therapy. In an effort to continue to look for applications to help women through the menopause transition and some of the devastating symptoms that go along with that transition, alternative hormone therapy, which is bioidentical and compounded bioidentical hormone therapy, was developed. Misconceptions about this alternative have become apparent due to unproven claims and celebrity endorsements. Through the evaluation of the literature, the information regarding traditional, bioidentical, and compounded bioidentical hormone therapy was identified and synthesized to answer the practice questions.

Best Practices. Menopausal symptoms which include depressive symptoms, anxiety, hot flashes, and sleep disturbances can be devastating and have lifelong consequences if not

adequately addressed. Based on the severity of the symptoms, a woman's quality of life can be adversely affected. Formby and Schmidt (2011) reported a significant fall in the Kupperman index and asserted that bioidentical hormone therapy demonstrates positive results of both physiological and clinical outcomes. The evidence is confusing; Gleason et al. (2015) identified oral hormone therapy does improve anxiety and depression however, transdermal bioidentical hormone therapy does not show benefits. Hormone therapy can be used for treatment of menopausal symptoms in women transitioning into menopause. Each form of hormone therapy, whether it is traditional or bioidentical, carries the same health risks. Therefore, the use of hormones should be prescribed at the lowest dose for the shortest duration possible for attempting to control menopausal symptoms.

As a woman ages, the risk of cardiovascular disease increases (World Health Organization, 2017). There is conflicting evidence available on benefit versus harm for estrogen therapy and coronary heart disease. The USPSTF (2017) brings to our attention the observational evidence about the protective effects of hormone therapy for heart health in younger women, however, also points out several seminal studies that have shown an increased risk of coronary heart disease due to hormone therapy in older postmenopausal women. Data reported from randomized clinical trials show no benefit of hormone therapy when used for cardiovascular disease in older postmenopausal women, rather a harmful effect due to an overall decline in the artery walls and build up of a fatty coating and scar tissue that increases the risk of thrombosis and decreased coronary circulation (USPSTF, 2017). Oral hormone therapy is metabolized through the liver, which creates a hepatic effect that increases cholesterol and coagulation parameters (Polac et al., 2013; Nii et al., 2015). These findings are associated with an increased risk of cardiovascular disease, which is predominantly higher when other co-morbidities exist

(Polac et al., 2013). Hormone replacement therapy should not be used to treat chronic conditions.

Farr et al. (2013) found that replacement hormone therapy significantly prevented loss of cortical bone. The United States Preventative Services Task Force (USPSTF) published a broad recommendation statement about the use of estrogen and progestin for chronic conditions in postmenopausal women. Within this recommendation statement, several studies are reviewed for evidence. The benefits are noted for the use of estrogen for postmenopausal osteoporosis. However, they go on to say that treatment should be prescribed at the lowest dose and for a brief period (USPSTF, 2017). Within their published report, The United States Preventative Services Task Force recommends other alternative medications and healthy living choices that do not carry the same health risks as hormone therapy for the use of postmenopausal osteoporosis (USPSTF, 2017). The individual benefits and risks need to be weighed each time a woman is seeking advice on menopause or any inherent genetic disease process.

Some of the studies based their findings on salivary lab results of women who were on the hormone replacement therapy. The American College of Obstetricians and Gynecologist (2012) point out concerns for safety and efficacy based on salivary testing and state "there is no evidence that hormonal levels in saliva are biologically meaningful and salivary testing does not currently offer an accurate or precise method of hormone testing" (p. 413). Recommendations for the use of traditional and transdermal "bioidentical" Food and Drug Administration approved hormone therapy for primary prevention of chronic conditions is discouraged due to the associated harm that they may cause. These harms and health risks are coronary heart disease, invasive breast cancer, thromboembolic events, decreased cognitive impairment, and gallbladder disease (USPSTF, 2017).

Current evidence regarding safety and efficacy. Literature articulated the theme of safety and purity of traditional, bioidentical, and compounded bioidentical hormone therapy. In a study assessing the effects of endogenous sex hormones on fibrinogen levels to estimate the effects of hormone therapy, Canonico et al. (2012) found a positive correlation of fibrinogen levels and estrogen levels, and significant interactions of total oestradiol (E2) with fibrinogen levels ($p<0.001$). Canonico et al. (2012) found the correlation of oestradiol (E2) with fibrinogen to be significantly more positive in women with an elevated body mass index (BMI) ($p = 0.02$). Increased fibrinogen levels are related to inflammation and are directly related to increased risk for cardiovascular disease (Canonico et al., 2012). Another safety concern around traditional hormone therapy is that of breast cancer. Increased breast density is a standalone risk factor for breast cancer. Carmona-Sanchez et al. (2013) reported a significant increase at five years in breast density in women on combined hormone therapy versus those on estrogen therapy alone ($p<0.009$). After five years of use, women on a cyclic combination of traditional hormone therapy had a significant increase in breast density versus women on continuous combined therapy ($p<0.039$).

Some traditional and transdermal "bioidentical" forms of hormone therapy have been approved for menopausal symptom management and are regulated by the Food and Drug Administration. Whedon et al.'s (2017) systematic review of ten different studies which compared bioidentical hormones with placeboes and included over 1,208 women, evaluated primary outcomes of improved depressive symptoms as measured by a validated depression scale. It was reported that there was no significant change in depressive symptoms in women who used bioidentical hormone therapy as compared to placebo (SMD-0.02, 95% CI -0.41 to +0.38). However, more than half of the subjects included were older postmenopausal women.

Adverse effects included increased vaginal bleeding. Whedon et al. (2017) reported that most of the studies included in the systematic review were of short duration and serious adverse effects were unable to be captured. In a study assessing the effects of bioidentical hormone therapy on menopausal symptoms of women in the menopause transition, Formby and Schmidt (2011) reported that after three and six months of use, saliva levels of estradiol and progesterone significantly increased as compared to baseline levels ($p<0.01$). Likewise, after six months of bioidentical hormone therapy treatment it was shown that the Kupperman index decreased to a value of 7 as compared to baseline value of 30 (Formby & Schmidt, 2011).

Other hormone therapy applications, such as compounded bioidentical hormone therapy, have no Food and Drug Administration approval. Due to the lack of Food and Drug Administration approval, guidelines for quality and safety are limited. Compounded bioidentical hormone therapy is not subjected to the same standards and lacks the regulatory testing of quality, purity, and potency (Bhavnani & Stanczyk, 2012). In fact, due to the lack of regulation of the compounded bioidentical hormone therapy, there have been proven cases of contamination by viruses, bacteria, and other pathogens (L'Hermite, 2017). Bhavnani and Stanczyk (2012) identify a report from the Food and Drug Administration Division of Prescription Drug Compliance and Surveillance where 34% of the products failed one or more standard quality tests; also nine out of ten products failed because the actual active ingredient was less than reported on the label. When products lack Food and Drug Administration approval, there is no class labeling or official labeling, which means compounded bioidentical hormone therapy is exempt from providing contraindications and warnings on the labels (The American College of Obstetricians and Gynecologists, 2012). The label of natural on compounded hormones does not

make them safer than the Food and Drug Administration approved hormones, they carry the same risks as other hormone preparations (“2 points to ponder”, 2016).

Current Trends

Due to the conflicting information about safety and efficacy, women are looking for an alternative. Supporters of custom-compounded bioidentical hormone therapy make unconfirmed claims that compounded bioidentical hormone therapy is safer and has fewer side effects (Bhavnani & Stanczyk, 2012). Thompson et al. (2017) found that women are frustrated and lack trust in traditional medicine; they felt clinicians who prescribed compounded bioidentical hormone therapy listened to them, and did not discount their symptoms or concerns. Also, they found that women felt empowered when choosing compounded bioidentical hormone therapy (Thompson et al., 2017). Fishman et al. (2017) point out that a "predominant complaint of women is that they felt misunderstood, minimized, and even dismissed" (p. 10).

Velentzis et al. (2016) conducted a survey study on Australian women to assess and estimate the current use of menopause hormone therapy. It was found that in 2013, the estimated use of hormone therapy in Australia was approximated at thirteen percent. In the United States, the use of traditional hormone therapy has decreased due to adverse findings from several terminal studies. However, the use of custom compounded bioidentical hormone therapy is reported to have increased. The increase may be due to unproven health claims, celebrity endorsements, and physician and pharmacist’s authorization while benefiting economically (Pinkerton & Santoro, 2015). In the US, prescriptions for compounded bioidentical hormone therapy cannot be tracked because the Food and Drug Administration does not regulate it; this means the actual number of compounded bioidentical hormone therapy users is unknown. Pinkerton and Santoro (2015) reported that approximately one to two and a half million US

women aged forty or older use compounded bioidentical hormone therapy, and spend approximately one to two billion US dollars each year on compounded bioidentical hormone therapy. Of the women surveyed, many reported not knowing that the Food and Drug Administration does not regulate compounded bioidentical hormone therapy, and several did not know if the hormone therapy they were using was compounded bioidentical hormone therapy or not (Pinkerton & Santoro, 2015). In another finding from a study done by Fishman et al. (2015), a surveyed participant stated: "they are more likely to use compounded bioidentical hormone therapy because it cannot be assigned a patent. Therefore, the pharmaceutical industry cannot make money from preparing it" (p. 13). This statement is entirely false and contrary to the actual truth of this multi-million dollar industry.

Gaps in the Literature

Due to the lack of Food and Drug Administration approval for compounded bioidentical hormone therapy, there are few rigorous studies done that include this form of hormone therapy. The well known terminal studies included bioidentical and traditional hormone therapy, although both of these forms had Food and Drug Administration approved. Two of the level III qualitative survey studies used convenience samples and lacked randomization of sample subjects, limited generalization to the population at large (Pinkerton & Santoro, 2015; Thompson et al., 2017). The USPSTF calls to our attention, a predominant number of the studies do not include different races or ethnicities (2017). The timing of initiation of hormone therapy has been mentioned, but there are conflicting data to support either harm or benefit, and it is not well understood (Espeland et al., 2017; USPSTF, 2017). Many of the studies do not take into account other co-morbidities of the participants, which could enhance the adverse effects of the HT. As in the

study by Canonico et al. (2012), it was found that overweight women had a more significant increase in fibrinogen levels than the leaner study participants.

Implications for Nursing Practice and Education

The evidence has pointed out the inconsistency and confusing information that is available to women about hormone therapy. Nurses working with women clients need to keep up-to-date on current data and research available to adequately inform and educate women on the efficacy and safety of hormone therapy. Also, it is essential to educate women on the changes and symptoms that can take place while transitioning through menopause. Across the board, every woman will experience menopause; however, not every woman will experience it the same way. Different cultures have divergent opinions and meanings for menopause (Indra, 2016). Helping women to understand the changes that their bodies are going through will equip them with knowledge so they can meet and react to the challenges of menopause positively. It is critical that women are offered current information on menopause and instructed on resources available to help with the symptoms with which they may be confronted. Nurses can inform on healthy lifestyle changes or modifications to manage menopausal symptoms. Nurses can ensure women have a voice in their care and that their concerns are heard. The topic of menopause, the transitional symptoms, and chronic conditions that women may experience with age need to be discussed and thought of as preventative medicine. How devastating are the symptoms? Women need to be informed of their choices and the evidence that exists. What types of hormone therapy are available? Even when the evidence can be confusing and conflicting, women need to be heard and educated on the benefits versus the harm of every therapy prescribed. Each option should be explored in partnership with the patient.

Recommendations for Nursing Research

Most of the studies included in this literature review recommend that more research needs to take place to evaluate the safety and efficacy of hormone therapy. It is essential to take into account the current recommendations from the United States Preventative Services Task Force, which advises against the use of hormone therapy as the primary prevention of chronic conditions in postmenopausal women (USPSTF, 2017). It is known that women are continuing to use hormone therapy. Increased research is needed to understand why they are choosing compounded bioidentical hormone therapy. Knowing why women are choosing hormone therapy or compounded bioidentical hormone therapy would offer information on how health care can integrate other practices or therapies to help women during this challenging life transition. Interventional nursing research is needed to look at alternatives to hormone therapy and the efficacy of substitute therapies. Of the users of hormone therapy, it was reported that the duration of use was significantly more than five years, which sparked recommendations to continue to monitor due to prolonged exposure and consequent health risks (Velentzis et al., 2016). More studies are needed to test compounded bioidentical hormone therapy preparations and the safety of use over extended periods.

Integration and Application of the Theory of Symptom Self-Management

Some of the symptoms of menopause can be devastating; depression and trouble sleeping can lead to other chronic conditions. Stephenson et al. (2013) found that stress and depression in women have been associated with declining health status, and have been shown to increase their risk of cardiovascular disease. Every woman experiencing menopausal symptoms reacts differently; some may perceive their symptoms as a threat or an unhealthy warning. Symptoms can be physical (hot flashes) as well as psychological (anxiety and depression). The Theory of

Symptom Self-Management (TSSM) can help care providers to implement positive self-efficacy for symptom self-management (Hoffman, 2013).

Using TSSM, understanding women's perceived self-efficacy is a crucial first step in identifying and addressing functions that can be applied to set goals for wellness and empowerment. A woman's menopausal symptoms may be sleep disturbances and anxiety. Addressing the physiological (menopausal transition and hormone fluctuation) and psychological (fatigue and anxiety symptoms), and how these symptoms may be affecting her day-to-day routine is part of the TSSM model. Sharing information and evidence on managing menopausal symptoms to help her set individual goals to handle her symptoms is the second step for Symptom Self-Management. Listening to the patient's perceptions of their ability to manage their symptoms, the nurse and care provider can direct the patient to set goals that are perceived by the patient as attainable to achieve symptom self-management. Each time the patient achieves a set goal and realizes the decreased negative symptoms will empower and encourage her for a positive health outcome.

The Theory of Symptom Self-Management can be applied to symptomatic menopausal women to help inform and empower them to make healthy lifestyle choices for symptom management. The nurse or healthcare provider needs to educate on non-hormonal treatments and lifestyle changes such as exercise, diet, and stress reduction. Pinkerton and Santoro (2015) reported that a large number of menopausal women did not seek hormone treatment, instead made lifestyle changes that they reported as producing moderate to significant relief of symptoms. Partnering with the patient to identify their symptoms and behaviors that they can modify (lifestyle changes), then applying it to functional goals and expected outcomes such as diet modification and exercise, will empower them to self-manage their symptoms.

Another enhancing intervention for self-efficacy and symptom self-management is to share professional websites such as the North American Menopause Society (NAMS) where the patient could find evidenced-based literature and information on menopause, healthy symptom management, and Food and Drug Administration approved pharmaceutical hormone therapy information. Support group engagement could help the patient to observe secondary experiences that would also promote self-efficacy and symptom self-management.

Many of the studies done to identify use, trends, and reasons why women choose hormone therapy or compounded bioidentical hormone therapy for the management of menopausal symptoms suggested a need for women to feel listened to, supported, and empowered (Pinkerton & Santoro, 2015 & Velentzis et al., 2016). The Theory of Symptom Self-Management promotes a trusting relationship and an engaged partnership with the patient to develop individualized health and symptom management with goal-oriented plans to empower them to optimal health outcomes (Hoffman, 2013).

Conclusion

This chapter discussed the common themes that emerged while conducting a critical review of the literature to answer the practice questions from chapter one. While it was shown that there are a variety of reasons women may choose to use hormone therapy, it also became evident that there is much confusing information available to the general public about hormone therapy, bioidentical, and compounded bioidentical hormone therapy. Many women are not well informed about the differences or the efficacy of the different forms (Pinkerton & Santoro, 2015). Governmental and professional organizations advise women to consult their physician or care provider when looking for information about hormone therapy. These organizations also provided strict recommendations for treatment, if necessary, due to family genetic osteoporosis

or severe menopausal symptoms, which include that treatment should be at the lowest dose for the shortest duration of time (USPSTF, 2017; The American College of Obstetricians and Gynecologists, 2012). Nursing implications were recommended for educating women on changes they may experience during menopause, current evidence of hormone therapy, and healthy lifestyle changes to help with the menopausal symptoms. Due to the growing popularity in compounded bioidentical hormone therapy, there is a need for research to evaluate the safety and efficacy of its use. The Theory of Symptom Self-Management was applied to show the importance of partnering with women to empower them with knowledge and evidence to help them live a long healthy life.

Appendix: Evidence Synthesis Matrix

<table>
<tr><td colspan="4">Source: Allen, A. J., McCubbin, J. A., Loveless, J. P., & Helfer, S. G. (2014). Effects of estrogen and opioid blockade on blood pressure reactivity to stress in postmenopausal women. Journal of Behavioral Medicine, 37(1). doi: 10.1007/s10865-012-9468-3</td></tr>
<tr><td>Purpose/Sample</td><td>Design (Method/Instruments)</td><td>Results</td><td>Strengths/Limitations</td></tr>
<tr><td>Purpose:
To explore if hormone replacement therapy has an effect on blood pressure while under stress, also comparing this to opioid antagonist results within the same group of participants.

Sample:
42 women total
27 HRT
15 placebo HRT

Setting: Quiet, temperature controlled room.

Johns Hopkins Evidence Appraisal

Level of Evidence:
Level I

Quality: B</td><td>Randomized Placebo controlled trial

Method: Participants were blinded to the drug versus placebo administration. Participants were given 12 week supply of HRT or placebo.

SBP, DBP, MAP, and HR were measured at baseline, during stressor task periods, and at a 10 minute post stress recovery period.

Instruments: Critikon Dinamap Model 8100 Vital Signs Monitor was used to measure HR, systolic, diastolic and mean arterial pressures.

A 10 minute computer based arithmetic stressor with randomly-generated arithmetic problems.</td><td>SBP significantly increased across all groups but the greatest increase was in the HRT/placebo group. Smallest increase was seen in the HRT/naltrexone group.

Conclusion:
Study provides support for the correlation between hormones and endogenous opioid function during stress.</td><td>Strengths:
Randomization and placebo used. Verified and validated instrument used for testing.

Limitations:
Did not allow for younger participants so these results may be different in younger women.</td></tr>
<tr><td colspan="4">Author Recommendations: Further studies are needed to address the differences that age may have on these results. Further studies are needed to investigate the merit of the findings within this study due to increased cardiovascular reactivity with older women.</td></tr>
<tr><td colspan="4">Implications: The study’s findings show how complex the effects of sex hormones are on the body systems.</td></tr>
</table>

Source: Canonico, M., Brailly-Tabard, S., Gaussems, P., Setiao, J., Rouand, O., Ryan, J.,… & Scarabin, P. (2012). Endogenous oestradiol as a positive correlate of plasma fibrinogen among older postmenopausal women: A population based study (the three-city cohort study). *Clinical Endocrinology*, *77*(6), 905-910.

Purpose/Sample	**Design (Method/Instruments)**	**Results**	**Strengths/Limitations**
Purpose: Assess the effects of sex hormones on the fibrinogen levels and those at higher cardiovascular and dementia risk. **Sample/Setting:** 602 postmenopausal women, aged 74 – 78 years old. **Johns Hopkins Evidence Appraisal** **Level of Evidence:** Level III **Quality:** B	Correlational study **Method:** Fasting blood samples of Fibrinogen, total E2 (estrogen), total T (testosterone) and SHBG (sex hormone binding globulin) from randomly selected participants. **Instrument:** Fasting blood samples of citrated and EDTA plasmas obtained. Fibrinogen was measured using the citrated plasma. Total E2, total T, and SHBG were measured using the EDTA plasma.	Positive correlation between levels of estrogen and levels of fibrinogen. No association shown between Testosterone, sex hormone binding globulin and fibrinogen. Overweight women had higher levels of estrogen and fibrinogen as compared to lean women. **Conclusion:** Higher levels of estrogen are associated with higher levels of fibrinogen which can promote inflammation in postmenopausal women.	**Strengths:** Number of participants in the study. **Limitations:** Could not rule out or explain the relationship to other health related comorbidities with the levels of estrogen and fibrinogen.

Author Recommendations:
More studies are needed to explore plasma fibrinogen and estrogen levels with respect to cardiac disease.

Implications: Fibrinogen is a factor in the coagulation process. Fibrinogen is also an inflammatory marker.

Source: Carmona-Sanchez, E., Duadros Lopez, J. L., Cuadros Celorrio, A. M., Perez-Roncero, G., Gonzalez Ramirez, A. R., & Fernandez Alonso, A. M. (2013). Assessment of mammographic density in postmenopausal women during long term hormone replacement therapy. *Gynecological Endocrinology, 29*(12), 1067-1070. doi: 10.3109/09513590.2013.831831			
Purpose/Sample	**Design (Method/Instruments)**	**Results**	**Strengths/Limitations**
Purpose: To assess the effects of long term hormone replacement therapy on mammographic (breast) density. **Sample/Setting:** **Sample:** 165 postmenopausal women receiving transdermal hormone therapy. **Setting:** Menopause Unit of the San Cecilio Clinical University Hospital, Granada, Spain. **Johns Hopkins Evidence Appraisal** **Level of Evidence:** Level II **Quality:** B	Quasi-experimental observational study. **Method:** Mammogram x-ray reports done at baseline, one year, and five years. **Instrument:** Standard mediolateral and craniocaudal mammogram projections obtained using X-ray equipment at one and five years.	At one and five years all women showed increased breast density. Women on combined HRT therapy showed a greater increased breast density than women on estrogen therapy alone. Women on a cyclic combined HRT therapy had the most significant increase in breast density at five years. **Conclusion:** Significant increase in breast density after combined estrogen and medroxyprogesterone acetate therapy than after estrogen alone. This finding is more frequently seen at five years of combined HRT treatment.	**Strengths:** Number of participants and number of follow-up years. **Limitations:** Was non-randomized study. Only used one form of progestin in HRT combination. Did not include diet of participants which could have had an effect on steroids within the body and breast characteristics.
Author Recommendations: Increased breast density is more frequent in women on combined HRT therapy than women on estrogen therapy alone.			
Implications: Increased breast density could hide or make it difficult to detect a small mass. Also, increased breast density is associated with the increased risk of breast cancer.			

Source: Espeland, M. A., Rapp, S. R., Manson, J. E., Goveas, J. S., Shumaker, S. A., Hayden, K. M.,… & Resnick, S. M. (2017). Long-term effects on cognitive trajectories of postmenopausal hormone therapy in two age groups. *Journals of Gerontology: Medical Sciences, 72*(6). doi:10.1093/Gerona/glw156

Purpose/Sample	**Design (Method/Instruments)**	**Results**	**Strengths/Limitations**
Purpose: Long term follow-up of two studies to determine if there are cognitive differences or late effects between placebo and intervention groups. **Sample:** Two large studies: Women's Health Initiative = 1,376 women aged 50 – 56 years old, and 2,880 aged 65-79 years old. **Setting:** 40 academic centers **Johns Hopkins Evidence Appraisal** **Level of Evidence:** Level I **Quality:** A	Systematic review with meta-analysis **Method:** Yearly phone interviews, data derived from 2008 – 2015. **Instruments:** East Boston Memory Test, Oral Trail Making Test, Verbal Fluency-Animals Test, and Digit Span Test. All data between intervention and placebo groups were compared using Statistical methods.	Slight and not significantly higher cognitive scores of younger women assigned hormone therapy. Placebo group of older women had significantly better score performance of global cognitive test. **Conclusion:** Hormone therapy started at menopause, in younger women, has no cognitive benefit or damage. Hormone therapy started in older women, results in small reduction in several cognitive functions that have been shown to persist.	**Strengths:** Large study with many participants over long term period. **Limitations:** Data were derived from volunteers so this may not be a good representation of the general population. Small detectable differences are reported, cannot rule out unmeasured factors that may have attributed to these differences.

Author Recommendations: Further assessment is needed to evaluate safety of hormone use in younger women.

Implications: Hormone use in older women has led to cognitive deficits that remain after medications are discontinued. As a woman ages, the brain adapts to loss of estrogen, and a secondary energy source is used. If estrogen is reintroduced at this time it will disrupt cognitive function.

Source: Farr, J. N., Khosla, S., Miyabara, Y., Miller, V. M., & Kearns, A. E. (2013). Effects of estrogen with micronized progesterone on cortical and trabecular bone mass and microstructure in recently postmenopausal women. *The Journal of Clinical Endocrinology & Metabolism, 98*(2), 249-257. doi: 10.1210/jc.2012-3406

Purpose/Sample	**Design (Method/Instruments)**	**Results**	**Strengths/Limitations**
Purpose: To examine if estrogen has an effect on cortical and trabecular bone. **Sample:** 76 menopausal women who had been previously enrolled in the KEEPS trial participated in this sub-study. **Setting:** Mayo Clinic, Rochester, Minnesota. **Johns Hopkins Evidence Appraisal** **Level of Evidence:** Level I **Quality:** A	Randomized Controlled Trial – sub study. **Method:** Double-blinded, four year study, 31 subjects received a placebo, 20 women received conjugated equine estrogen, and 25 women received transdermal 17B-estradiol with pulsed micronized progesterone. **Instruments:** High-resolution peripheral quantitative computed tomography (HRpQCT).	Menopausal hormone therapy significantly prevented loss of cortical bone. Menopausal hormone therapy did not prevent decrease in trabecular bone parameters. **Conclusion:** Cortical bone is responsive to estrogen therapy.	**Strengths:** Used 3 dimensional imaging with computed tomography (QCT) which has much more validity than other studies that used x-ray. **Limitations:** Used a calculated four year percentage rate of change for one of the measurements due to the technique of data appraisal that overestimated the initial calculation.

Author Recommendations: More studies and investigation into the site specific effects of hormone therapy on bone and dose-dependent response trials are needed. Optimal estrogen dose therapy based on individualized risk assessment is required.

Implications: Estrogen therapy can maintain cortical bone which can prevent fractures.

<table>
<tr><td colspan="4">Source: Fishman, J. R., Flatt, M. A., & Settersten, R. A. (2015). Bioidentical hormones, menopausal women, and the lure of the “natural” in U.S. anti-aging medicine. Social Science Medicine, 132, 1-21. doi: 10.1016/j.socscimed.2015.02.027.</td></tr>
<tr><td>Purpose/Sample</td><td>Design (Method/Instruments)</td><td>Results</td><td>Strengths/Limitations</td></tr>
<tr><td>Purpose: To investigate clinician’s practice and views of aging and medicine, also investigate patient perceptions and experience with anti-aging therapies.

Sample:
32 clinicians
25 women

Setting: Phone interview

Johns Hopkins Evidence Appraisal

Level of Evidence:
Level III
Quality: B</td><td>Qualitative

Method: Interview

Instrument:
Phone interviews of clinicians about aging and medicine. Phone interviews of patients regarding anti-aging therapies.</td><td>Two interrelated reasons of the study were that the women of the study actually used BHRT and the clinicians actually prescribed BHRT. The second connection was the reason the women had started using the BHRT, which was frustration with “traditional” physicians.

Conclusion: Overall emphasis that BHRT is natural and safe. BHRT helps a woman to stay young and healthy. BHRT helps with menopausal symptoms.</td><td>Strengths: Represents a view of both clinician and patient.

Limitations: small participation size. The women were actual patients of the clinicians.</td></tr>
<tr><td colspan="4">Author Recommendations: Did not want to come to a positive or negative conclusion but rather understand why clinicians and patients are drawn to the use of BRHT</td></tr>
<tr><td colspan="4">Implications: Women are drawn to BRHT and the clinicians who prescribe because they felt like the clinicians listen to them and validated their concerns and menopausal symptoms. The clinicians that prescribe BRHT regard themselves as good listeners and that they have the ability to care holistically.</td></tr>
</table>

Source: Formby, B. & Schmidt, F. (2011). Efficacy of biorhythmic transdermal combined hormone treatment in relieving climacteric symptoms: A pilot study. *International Journal of General Medicine, 4*, 159- 163. doi: 10.2147/IJGM.S16139			
Purpose/Sample	**Design (Method/Instruments)**	**Results**	**Strengths/Limitations**
Purpose: To evaluate if a cyclic dose of hormone treatment can relieve climacteric symptoms of menopausal women. **Sample:** 29 healthy, non-hysterectomized women (age 44 – 56 years, mean 51 years). **Setting:** Santa Barbara, California, USA. **Johns Hopkins Evidence Appraisal** **Level of Evidence:** Level II **Quality:** B	Quasi-Experimental, randomized with intervention, no control. **Method:** Saliva and serum values prior to treatment, at three, six months, and at different times before and after cream application. Menopausal symptom were evaluated with a questionnaire prior to treatment, at three, and six months. **Instruments:** High-performance liquid chromatography (HPLC). Kupperman index.	After three and six months, saliva levels of estrogen and progesterone significantly increased along with a significant fall in Kupperman index. **Conclusion:** Bioidentical hormone therapy at cyclical cycles, that mimic the secretory 28-day pattern of a healthy, menstruating woman, demonstrates positive results of both physiological and clinical outcomes. It was demonstrated that hormone therapy has a positive effect on climacteric symptoms of menopausal women.	**Strengths:** Randomization. All subjects completed the study. Correlations are shown by increase in serum and saliva levels of hormones and positive effects on climacteric symptoms. **Limitations:** No control or placebo. Sampling was done using the most convenient solution which is saliva and then compared to serum concentrations.
Author Recommendations: Larger studies over long-term are needed to determine long standing effects of bioidentical hormone therapy.			
Implications: Sleep difficulties and depressive symptoms are often seen in menopausal women. Estrogen has been shown to control circadian rhythms and improve sleep and depressive symptoms.			

<table>
<tr><td colspan="4">Source: Gleason, C. E., Dowling, N. M., Wharton, W., Manson, J. E., Miller, V. M., Atwood, C. S.,… & Asthana, S. (2015). Effects of hormone therapy on cognition and mood in recently postmenopausal women: Findings from the randomized controlled KEEPS-cognitive and affective study. PLOS Medicine, 12(6), 1-25. doi: 10.1371/journal.pmed.1001833</td></tr>
<tr><td>Purpose/Sample</td><td>Design (Method/Instruments)</td><td>Results</td><td>Strengths/Limitations</td></tr>
<tr><td>Purpose:
To identify if there are cognitive and mood effects related to use of menopausal hormone therapy (MHT).

Sample:
693 women in late menopausal transition and early postmenopausal periods.

Setting:
University of Wisconsin-Madison.

Johns Hopkins Evidence Appraisal

Level of Evidence:
Level I
Quality: A</td><td>Randomized Control Trial, in conjunction with parent KEEPS trial.

Method: Participants were randomized into three groups; oral conjugated equine estrogens (o-CEE), transdermal estradiol (t-E2), or placebo.

Instruments:
Cognitive and mood assessment data collected at baseline, months 18, 36, and 48. Cognitive assessment included global cognitive measure and four domain scores. This test was selected because it was used in another large study the WHIMS. Mood was assessed using The Profile of Mood States (POMS) a survey to rate 65 adjectives on a five-point Likert scale.</td><td>o-CEE group had clinically significant change at month 48 on POMS depression and anxiety.
Placebo and t-E2 groups showed no improvements.
Global cognitive performance did not differ between groups.

Conclusion:
Menopausal hormone therapy does not improve cognition.
Oral hormone therapy does improve anxiety and depression, transdermal does not show benefits.</td><td>Strengths:
Randomization into groups and control group. Consistent results. Consistent recommendations. Good references and comparisons to other large studies. Length of study was four years.

Limitations: The results cannot be inferred past four years of treatment. It has been shown that longer use of HT can increase risk of adverse effects. Generalized due to the population of study, not a representation of general postmenopausal US population. None of the women in study had a hysterectomy. Not long enough of a trial to assess dementia.</td></tr>
<tr><td colspan="4">Author Recommendations: Use this data to inform women who are considering menopausal hormone therapy. More studies and investigation is needed into the variations in dose, hormone formulation, and route of administration specifically examining the safety of use.</td></tr>
<tr><td colspan="4">Implications: With the help of their provider and with current evidence, women can make an informed decision as to whether or not they would benefit from menopausal hormone therapy.</td></tr>
</table>

Source: Iftikhar, S., Shuster, L. T., Johnson, R. E., Jenkins, S., & Wahner-Roedler, D. L. (2011). Use of bioidentical compounded hormones for menopausal concerns: Cross-sectional survey in an academic menopause center. *Journal of Women's Health, 20*(4), 559–564. doi: 10.1089/jwh.2009.1915

Purpose/Sample	**Design (Method/Instruments)**	**Results**	**Strengths/Limitations**
Purpose: To assess the popularity of BCH, to understand beliefs, practices, and self-described clinical outcomes. **Sample:** 184 consecutive women seeking consultation for menopause. **Setting:** Mayo Clinic, Women's Health Clinic in Rochester, Minnesota. **Johns Hopkins Evidence Appraisal** **Level of Evidence:** Level III **Quality:** B	Nonexperimental; survey research **Method:** Convenience Sample of 208 consecutive participants surveyed about bioidentical compounded hormone knowledge. **Instrument:** 19 Item survey; self-report.	20% of the women surveyed used BCH and nearly 50% of the women surveyed were familiar with BCH. No clear differences were reported between BCH and CHT use on menopausal symptoms. BCH users tended to respond positive about memory and fatigue concerns. 67% of surveyed thought BCH was safer than CHT. **Conclusion:** The rate of use was greater than expected. Because of the media reports and notions that BCH is natural there is a tendency to believe it is safer than CHT. BCH = Bioidentical Compounded Hormone Therapy. CHT = Conventional Hormone Therapy.	**Strengths:** sample size, with an 88% responds rate. **Limitations:** Circumstantial and exploratory. Survey was not validated in advance of the study. Short duration of one year.

Author Recommendations: Further studies are needed, it is important to advance our understanding as to why women seek this treatment and what their experiences have been.

Implications: Wide variety of U.S. Food and Drug Administration approved and non-approved hormones with differing class effects, molecular structure, origin, potency, specificity, bioavailability, and routes of administration. There is a lack of evidence about each product especially non-approved compounded preparations.

Source: Kocoska-Maras, L., Radestad, A. F., Carlstrom, K., Backstrom, T., Schoultz, B. O., & Hirschberg, A. L. (2013). Cognitive function in association with sex hormones in postmenopausal women. *Gynecological Endocrinology, 29*(1), 59–62. doi: 10.3109/09513590.2012.705385			
Purpose/Sample	**Design (Method/Instruments)**	**Results**	**Strengths/Limitations**
Purpose: To investigate if there is a relationship between cognitive function and serum levels of sex hormones. **Sample:** 200 naturally postmenopausal women between 50 – 65 years old. **Setting:** Stockholm, Sweden **Johns Hopkins Evidence Appraisal** **Level of Evidence:** Level: I **Quality:** B	Randomized Control Trial **Method:** Participants were randomly assigned to estrogen, testosterone or placebo treatment for 1 month. Cognitive tests were performed at the end of the treatment time. Blood samples were drawn before beginning hormone therapy and at the end of treatment. Cognitive test was measured by a mental rotation test. Verbal fluency was tested by amount of words written in a 1 minute time frame. Verbal memory was tested by using free recall. **Instruments:** Correlations between hormone levels and cognition were assessed using the Spearman rank correlation test. Serum analyses were completed using commercial kits from Siemens Medical Solutions.	Negative associations found in fluency, spatial and verbal ability in all treatment groups except the placebo group which found a positive correlation with verbal fluency. **Conclusion:** Hormone therapy does not increase fluency, spatial, or verbal ability.	**Strengths:** Large number of participants in study. **Limitations:** Women in the estrogen treated group were slightly older than women in the other two groups. No support for cognitive test validity. Short term trial.
Author Recommendations: Study results **s**upport the hypothesis of the importance in a balance between estrogen and testosterone for attaining optimal spatial and verbal abilities.			
Implications: There are several estrogen receptors within the brain.			

Source: Nii, S., Shinohara, K., Matsushita, H., Noguchi, Y., Watanabe, K., & Wakatski, A. (2015). Hepatic effects of estrogen on plasma distribution of small dense low-density lipoprotein and free radical production in postmenopausal women. *Journal of Atherosclerosis and Thrombosis, 23*(7), 810-818.

Purpose/Sample	**Design (Method/Instruments)**	**Results**	**Strengths/Limitations**
Purpose: To investigate the hepatic effects of three different types and different routes of estrogen administration on levels of cholesterol production. **Sample:** 45 healthy Japanese postmenopausal women **Setting:** Department of Obstetrics and Gynecology, Aichi, Medical University **Johns Hopkins Evidence Appraisal Level of Evidence:** Level I **Quality:** B	Randomized Controlled Trial For three months 15 subjects received oral estrodiol 0.625 mg per day, 15 subjects received transdermal 50 mcg estrodiol per day, and 15 subjects received oral 1 mg estrodiol per day. **Instruments:** Vital signs and blood samples were measured at the start of the study and then after the 3 months of hormone treatment. Blood samples consisted of serum triglycerides, LDL, total cholesterol, and HDL.	In all groups it was comparatively found that climacteric symptoms improved for all groups. CEE – significantly reduced total cholesterol and LDL, and significantly increased HDL and triglycerides levels. Oral estrodiol– significant increase in HDL Transdermal estrodiol – significantly decreased the triglyceride level **Conclusion:** Different hepatic effects can be seen with different routes and doses of estrogen. These different effects may be associated with the risk of cardiovascular disease because of the distribution effect of LDL and the free radical production.	**Strengths:** Randomized to treatment. **Limitations:** Small study size. Short duration of study time.

Author Recommendations: Further studies are needed to demonstrate Oral versus transdermal effects.

Implications: When the liver is stimulated it produces more triglycerides which can lead to an increased risk of CVD.

Source: Pingel, J., Langber, H., Skovgard, D., Koskinen, S., Flyvbjerg, A., Frystyk, J.,… & Hansen, M. (2012). Effects of trandermal estrogen on collagen turnover at rest and in response to exercise in postmenopausal women. *Journal of Applied Physiology, 113*(7). doi:10.1152/jappiphysiol.01463.2011.			
Purpose/Sample	**Design (Method/Instruments)**	**Results**	**Strengths/Limitations**
Purpose: To assess if there is an effect on collagen and skeletal muscle when exposed to hormone therapy while exercising and resting. Also, to assess if transdermal hormone therapy effects the levels of insulin like growth factors. **Sample:** Eleven, y postmenopausal women aged 60 years or older. **Setting:** Institute of Sport Medicine, Bispebjerg Hospital, Copenhagen, Denmark. **Johns Hopkins Evidence Appraisal Level of Evidence:** Level I **Quality:** C	Randomized Controlled, Crossover Trial **Method:** Randomized to start estrogen hormone therapy transdermal patches along with prescribed exercise and rest. Blood, urine, and dialysate examined at day two, three, and five. Different exercises were prescribed. **Instruments:** Blood Serum, urine and dialysate samples examined for levels of hormone, collagen, and growth factor.	Serum estrogen increased significantly in hormone group. Significant effect between time and treatment observed, at day five serum collagen markers were significantly higher. Plasma collagen marker also had a significant increase over time. Post-exercise insulin like growth factor increased as compared to pre-exercise level. **Conclusion:** A combination of exercise and short term hormone replacement therapy increase collagen production.	**Strengths:** Randomization and control group. **Limitations:** Small number of participants. Short time frame for study. Missing samples during testing periods.
Author Recommendations: More studies needed with more time points to detect further collagen changes. Placement of the hormone patch is important to receive the best effects of the therapy.			
Implications: It has been shown that muscle and bone mass are reduced as a woman ages. Collagen is part of the structural protein in tendons and ligaments. Estrogen can be used to stimulate collagen production which may help with muscle recovery after strenuous exercise, and with bone collagen synthesis.			

Source: Pinkerton, J. V., & Santoro, N. (2015). Compounded bioidentical hormone therapy: Identifying use trends and knowledge gaps among US women. *Menopause, 22*(9), 926-936. doi: 10.1097/GME.0000000000000420			
Purpose/Sample	**Design (Method/Instruments)**	**Results**	**Strengths/Limitations**
Purpose: To assess the knowledge of the difference between compounded hormone therapy versus Food and Drug Administration (FDA) approved hormone therapy, to measure the use of these therapies, and also to acquire information on menopausal experience. **Sample:** Harris Survey: 801 women Rose Survey: 2044 **Setting:** Internet, web based, United States. **Johns Hopkins Evidence Appraisal Level of Evidence:** Level III **Quality:** A	Nonexperimental; survey research **Method:** Two different surveys were completed through the internet. Harris: Surveyed women aged 45 – 60 years old who were currently or previously experiencing menopause symptoms. Rose: Surveyed women aged 40 years or older who currently or prior use hormone therapy.	Harris: two percent had used compound hormone therapy. 14% had correct knowledge about compound hormone therapy. 76% were unsure of the correct answer. Rose: twenty-one percent reported current or prior use. 27% did not know if their hormone therapy was compounded or personalized for them. **Conclusion:** Compounded hormone therapy use is higher in younger age groups.	**Strengths:** Number of participants. Consistent results. **Limitations:** Estimations and generalizations of the population on current use of compounded hormone therapy – not a true number. No randomization.
Author Recommendations: Women considering hormone therapy should seek advice from their physician. Physicians can educate on evidence that support the efficacy, safety, and quality of compounded hormone therapy or Food and Drug approved hormone therapy.			
Implications: Estimated that 1 – 2.5 million US women take compounded hormone therapy but not all understand or are aware of the difference between FDA approved or compounded hormone therapy. There can be a difference in quality among the variations of compounded hormone therapy and safety is a concern.			

Source: Połac, I., Borowiecka, M., Wilamowska, A., & Nowak, P. (2013). Coagulation and fibrynolitic parameters in women and the effects of hormone therapy; comparison of transdermal and oral administration. *Gynecological Endocrinology, 29*(2), 165–168. doi: 10.3109/09513590.2012.730567			
Purpose/Sample	**Design (Method/Instruments)**	**Results**	**Strengths/Limitations**
Purpose: To assess the effects of oral versus transdermal hormone therapy on coagulation and fibrinolitic parameters. **Sample:** 54 postmenopausal women **Setting:** Department of Gynecology and Menopausal Disorders, Polish Mother's Memorial Hospital—Research Institute in Lodz, Poland **Johns Hopkins Evidence Appraisal Level of Evidence:** Level II **Quality:** B	Quasi Experimental **Method:** Blood samples were collected analyzed for total clot formation and fibrinolysis which included; platelet count, activated partial thromboplastin time, and thrombin inhibitor of fibrinolysis. **Instruments:** Serum blood tests.	After six months the level of Fg was higher in the HT group. Transdermal route of HT had less of an effect on hemostatic levels overall. No significant difference in Plt, APTT, and triglycerides among all three groups. Thrombin activity was statistically higher in HT group. **Conclusion:** There is a difference in effect of hormone therapy on clotting factors between oral and transdermal products.	**Strengths:** Intervention and control groups. **Limitations:** Lacks random assignment to groups. Small study group participation.
Author Recommendations: The goal of hormone therapy selection for climacteric complaints should be to choose the safest product with the lowest known changes in coagulation and fibrinolysis markers. More studies are needed to look at efficacy and safety.			
Implications: As women age the risk of cardiac disease increases. Hormone therapy has been shown to increase arterial and venous thrombosis which can add to the risk of cardiovascular disease in older women.			

Source: Ran, S. Y., Yu, Q., Chen, Y., & Lin, S. Q. (2017). Prevention of postmenopausal osteoporosis in Chinese women: A 5-year, double-blind, randomized, parallel placebo-controlled study. *Climacteric, 20*(4), 391-396. doi:10.1080/13697137.2017.1325469			
Purpose/Sample	**Design (Method/Instruments)**	**Results**	**Strengths/Limitations**
Purpose: To assess if hormone therapy is safe and effective in preventing bone loss in Chinese Women during early menopause and evaluate if there are any long term effects. **Sample:** 120 total women participants aged 40 – 55 years old. 60 in the menopausal transition group and 60 in the early menopause group. **Setting:** China **Johns Hopkins Evidence Appraisal** **Level of Evidence:** Level I **Quality:** A	Randomized Controlled Trial **Method:** Estradiol valerate and medroxyprogesterone acetate tablets were used for the hormone therapy. Starch tablets were used for the placebo. All participants received twice-daily calcium and vitamin D supplements and participated in a standard exercise program of fast walking for 10 minutes a day. **Instrument:** Dual-energy x-ray absorptiometry, bone indexes, serum, and urine tests at beginning, 12, 24, 36, 48 and 60 months. Radiographs of the thoraci and lumbar vertebra were taken at beginning, 48, and 60 months.	Significant increase in bone mass density was seen in hormone groups over the first two years but then continued to decrease but remain higher than baseline. Placebo group had a slight increase at first year and then a significant decrease over the five years. At the end of the fifth year bone mass density remained higher than before treatment for the hormone groups. **Conclusion:** Estrogen and progesterone hormone therapy can increase bone mineral density for women in early menopause and sustain bone mineral density during menopausal transition.	**Strengths:** Length of study. Controlled with intervention. Solid results. **Limitations:** Narrow population group studied. Only studied one form of oral estrogen with progesterone.
Author Recommendations: More studies needed to evaluate effectiveness and safety of long term effects of hormone replacement therapy for prevention of osteoporosis.			
Implications: Postmenopausal women have been shown to have a loss of bone mass due to low estrogen levels.			

Source: Ruiz, A. D. & Daniels, K. R. (2014). The effectiveness of sublingual and topical compounded bioidentical hormone replacement therapy in post-menopausal women: An observational cohort study. *International Journal of Pharmaceutical Compounding, 18*(1), 70-77.			
Purpose/Sample	**Design (Method/Instruments)**	**Results**	**Strengths/Limitations**
Purpose: Assess if sublingual and topical compounded bioidentical hormone replacement therapy is effective for the treatment of vasomotor, mood, and other quality-of-life symptoms for postmenopausal women. **Sample:** 200 Women received sublingual or topical bioidentical hormone replacement therapy. Mean age of the participants was 52 years old. **Setting:** San Antonio, Texas. **Johns Hopkins Evidence Appraisal Level of Evidence:** Level II **Quality:** B	Quasi Experimental - Observational Cohort Study. **Method:** Survey, self report at start of therapy and at three and six months. **Instrument:** Microsoft Corp Austin, Texas software was utilized to create a survey form. Survey was administered by a train professional pharmacist.	Participants receiving sublingual hormone replacement had the most significant reduction in symptoms. **Conclusion:** Oral sublingual hormone therapy had faster and more significantly improved outcomes versus topical therapy. Over longer periods of use there can be small improvements in mood and night sweats seen with topical therapy.	**Strengths:** Consistent data. **Limitations:** Narrow demographics of study participants. Rater bias is present because of the way the data was collected.
Author Recommendations: More studies needed to evaluate BHRT in combination with testosterone. More studies are needed to test compounded bioidentical hormone therapy preparations.			
Implications: This study examined pharmaceutical FDA approved bioidentical sublingual and topical hormone medications.			

Source: Sood, R., Warndahl, R. A., Schroeder, D. R., Singh, R. J., Rhodes, D. J., Wahner-Roedler, D.,… & Shuster, L. T. (2013). Bioidentical compounded hormones: A pharmacokinetic evaluation in a randomized clinical trial. *Maturitas, 74*(4), 375-382. doi: 10.1016/j.maturitas.2013.01.010

Purpose/Sample	**Design (Method/Instruments)**	**Results**	**Strengths/Limitations**
Purpose: To compare estrogen and progesterone levels obtained after the use of bioidentical preparations and conventional hormone therapy. **Sample:** 40 Postmenopausal women **Setting:** Rochester, MN **Johns Hopkins Evidence Appraisal** **Level of Evidence:** Level I **Quality:** B	Experimental, randomized controlled trial. **Method:** Blood samples drawn on study day one, fifteen, sixteen. Women were randomized to one of four treatment arms. Estradiol-estril cream (Bi-est), placebo skin patch, and compounded oral micronized progesterone capsules. Estradiol-containing patch (Vivelle-dot), placebo cream, and commercially available oral micronized progesterone capsules (prometrium)	The Bi-est 2.5 and 3 mg provided a lower estrogen level as compared to the Vivelle-Dot patch. Estrogen absorption with Bi-est creams highly variable and not consistent peak of absorption. Compounded progesterone cream and capsule had comparable levels in all four groups. **Conclusion:** The small increases in estradiol levels from the Bi-est formula raises a question as to whether the reported symptom relief is due to the dose or a placebo effect.	**Strengths:** Randomization of assignment. **Limitations:** Choice of formulas was experimental due to lack of evidence-based guidelines. Small study size.

Author Recommendations: Due to the low estrogen level raises from the bioidentical compounded formulations; there is uncertainty of a bone benefit, more studies are needed.

Implications: The term Bioidentical refers to a medication being like a human component, this in turn leads to the belief that it is safe, and has led to an increase in popularity and use of bioidentical hormones. Differences in serum levels may be explained by the individual variations in skin physiology, blood flow, and hormone metabolism.

Source: Stephenson, K., Neuenschwander, P. F., & Kurdowska, A. K. (2013). The effects of compounded bioidentical transdermal hormone therapy on hemostatic, inflammatory, immune factors; cardiovascular biomarkers; quality-of-life measures; and health outcomes in perimenopausal and postmenopausal women. *International Journal of Pharmaceutical Compounding*, *17*(1*)* 74–85.

Purpose/Sample	**Design (Method/Instruments)**	**Results**	**Strengths/Limitations**
Purpose: Examine the long-term effects of compounded bioidentical transdermal hormone therapy on cardiovascular biomarkers, hemostatic, inflammatory, immune signaling factors; quality-of-life measures; and health outcomes. **Sample:** 75 women in menopausal transition and postmenopausal period. **Setting:** **Johns Hopkins Evidence Appraisal** **Level of Evidence:** Level II **Quality:** B	Quasi-experimental Study. **Method:** Initial baseline blood samples and assessment including vital signs, at 2 months, and annually for 36 months. Instruments: Factor VII, fibrinogen, antithrombin III, inflammatory and immune signaling factors, sex steroid levels. Also Green Climacteric scale, Hamilton anxiety and depression scale, and Holmes Rahe stress scale used.	Statistically significant changes in inflammatory and immune signaling factors seen with transdermal hormone therapy. Statistically significant decreases in Greene Climacteric Scale. Fasting glucose and triglycerides decreased significantly. **Conclusion:** Study supports the use of compounded transdermal bioidentical hormone replacement therapy.	**Strengths:** Randomization to therapy. **Limitations:** No control, no group tested with placebo.

Author Recommendations: Compounded transdermal BHRT should be considered safe and effective therapy for menopausal symptoms.

Implications: Other studies claim that BHRT can have the same effect as medroxyprogesterone acetate and conjugated equine estrogen, this specific study does not support this claim.

Source: Thompson, J. J., Ritenbaugh, C. & Nichter, M. (2017). Why women choose compounded bioidentical hormone therapy: Lessons from a qualitative study of menopausal decision-making. *Bio Medical Central Women's Health, 17*(1). doi: 10.1186/s12905-017-0449-0			
Purpose/Sample	**Design (Method/Instruments)**	**Results**	**Strengths/Limitations**
Purpose: To Identify the reasons women choose to use compounded bioidentical hormone therapy CBHT. **Sample/Setting:** Twenty-one women, current or previous users of CBHT. **Johns Hopkins Evidence Appraisal** **Level of Evidence:** Level III **Quality:** B	Qualitative Study **Method:** Semi-structured focus groups and interviews lasting 90 – 120 minutes. **Instruments**: Audio recorded and transcribed verbatim.	All twenty-one women felt **pushed** away due to overall frustration with traditional medicine mainly due to lack of trust, dismissing their concerns, and seen as relying on pharmaceuticals to treat symptoms. Lack of trust in conventional HT due to media reports of cancer. **Push and Pull:** 17 of the 21 (81%) said they had tried herbal formulas to help with menopausal symptoms but it did not help. Pull: three key themes to CBHT; it is effective, it is safe, and it is tailored to my individual body. **Conclusion:** Women choose CBHT because they consider them safer, the clinician listens to them and does not discount their symptoms or concerns. Also, the women feel as if they have power and a voice when choosing CBHT.	**Strengths:** Opinions and beliefs of CBHT past users. Highly educated women were participants in this study. Several of the participants had health related careers. Conclusions are well supported with other evidence. **Limitations:** Small study size, may not be a true representation of the general population.
Author Recommendations: More studies understanding why women choose CBHT are needed. Women would benefit from being able to voice concerns, symptoms, and preference of treatment and also have an opportunity for a clinician to address the benefits and risks of all hormone therapy options.			

Implications: Data has been published that indicates CBHT use has increased even though there are FDA approved bioidentical hormone therapy products

Source: Velentzis, L. S., Banks, E., Sitas, F., Salagame, U., Tan, E. H., & Canfell, K. (2016). Use of menopausal hormone therapy and bioidentical hormone therapy in Australian women 50 to 69 years of age: Results from a national, cross-sectional study. *PLOS One, 11*(3), 1-12. doi: 10.1371/journal.pone.0146494

Purpose/Sample	Design (Method/Instruments)	Results	Strengths/Limitations
Purpose: To assess and estimate current use of menopause hormone therapy and bioidentical hormone therapy in Australian women aged 50 – 69 years of age. **Sample:** 4,389 participants returned completed questionnaires. **Setting:** Australia **Johns Hopkins Evidence Appraisal** **Level of Evidence:** Level III **Quality:** A	Non- experimental study. Population based survey **Method:** Survey – self report. **Instrument:** Validated MHT-related questionnaire.	Current use of MHT = 13%, duration of use <5 years was 27% and >5 years 73% and this increased with age. Most MHT current users reported using oestrogen only. BHT current use was 2%. Combined use of BHT + MHT = 15%. **Conclusion:** Women are using more menopausal hormone therapy then bioidentical hormone therapy.	**Strengths:** Large sample size. Random selection of participants. The use of the validated MHT-related questionnaire. Data correlation with other studies. **Limitations:** Low rate of completed questionnaires – only 22%. Generalization of the population. Self-reported data used.

Author Recommendations: Continued monitoring of the use of MHT and BHT is needed.

Implications: From past studies it has been established that MHT is effective for treatment of menopausal symptoms but is recommended for use at the shortest duration and should not be used for prevention of chronic diseases. BHT is not subject to the same regulatory controls as MHT.

<table>
<tr><td colspan="4">Source: Whedon, J. M., KizhakkeVeettil, A., Rugo, N. A., & Kieffer, K. A. (2017). Bioidentical estrogen for menopausal depressive symptoms: A systematic review and meta-analysis. Journal of Women's Health, 26(1), 18–28. doi: 10.1089/jwh.2015.5628</td></tr>
<tr><td>Purpose/Sample</td><td>Design (Method/Instruments)</td><td>Results</td><td>Strengths/Limitations</td></tr>
<tr><td>Purpose:
Assess the effectiveness and safety of bioidentical estrogens for treatment of depression in peri and postmenopausal women.

Sample/Setting:
10 included studies with 1208 subjects

Johns Hopkins Evidence Appraisal

Level of Evidence:
Level I
Quality: A</td><td>Systematic review of RCTs, with meta-analysis.

Randomized controlled trials investigating menopausal women who sought HT for treatment of reported depressive symptoms.

Literature search from databases: CINAHL, PubMed, Medline, and the Cochrane Library.</td><td>Within the 10 included studies there was no significant difference in the treatment group versus the placebo group for change in depressive symptoms.

Secondary outcomes: five of the studies reported a significant decrease in vasomotor symptoms for the treatment group using estradiol.

Adverse events: three studies reported increased vaginal bleeding in the treatment group that were using bioidentical estrogens.

Conclusion:

There is no significant evidence to support the use of bioidentical estradiol for menopausal depressive symptoms.</td><td>Strengths:
Randomization, interventions, and control. Large amount of study subjects.

Limitations:

Most of the included studies were of short duration. All studies included investigated only one form of HT; bioidentical estradiol.</td></tr>
<tr><td colspan="4">Author Recommendations: More studies are needed that assess different types and combinations of bioidentical HT and nonbioidentical HT for the effectiveness of menopausal depressive symptoms.</td></tr>
<tr><td colspan="4">Implications: A better understanding of risks and benefits of bioidentical HT would help women to be able to make a more educated decision when choosing HT.</td></tr>
</table>

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