



Prescribing habits for hormone replacement therapy in Montana practitioners  
by Sherri Lynn Nassar

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Nursing  
Montana State University

© Copyright by Sherri Lynn Nassar (2004)

**Abstract:**

This study sought to examine the change in prescribing habits for hormone replacement therapy (HRT) in Montana practitioners since the publication of the Women's Health Initiative (WHI). **STUDY DESIGN:** A random sample of 160 Montana physicians, nurse practitioners, and physician assistants in the field of women's health were selected to receive a survey examining the effects of the WHI on their current and past prescribing habits. **RESULTS:** 53% of the sample returned the survey. Ninety-seven percent of the respondents were familiar with the WHI results, with 88% reporting that the results had a significant impact on their prescribing. Ninety-eight percent reported using HRT for menopausal symptoms, and only 4% currently use HRT for cardiovascular protection. This compares with 57% of respondents using HRT for cardiovascular protection prior to the WHI results. Ninety-four percent of the respondents report using other modalities for treating hot flashes and 96% use other modalities for osteoporosis treatment and prevention. Currently, most of the respondents are recommending that women use HRT for 1-5 years or for not set time. The results showed that the WHI had the most impact on those in practice greater than 10 years. Finally, there were very few differences in results when the data was analyzed based on specialty area, gender, or professional designation. **CONCLUSIONS:** This study demonstrated that the Women's Health Initiative results had a significant impact on participating Montana practitioners. It also showed that the providers in Montana are following national trends for HRT use and have quickly responded to new evidence in the women's health arena.

PRESCRIBING HABITS FOR HORMONE REPLACEMENT THERAPY IN  
MONTANA PRACTITIONERS

by

Sherri Lynn Nassar

A thesis submitted in partial fulfillment  
of the requirements for the degree

of

Master of Nursing

MONTANA STATE UNIVERSITY  
Bozeman, Montana

June 2004

N378  
N187

APPROVAL

of a thesis submitted by

Sherri Lynn Nassar

This thesis has been read by each member of the thesis committee and has been found to be satisfactory regarding content, English usage, format, citations, bibliographic style, and consistency, and is ready for submission to the College of Graduate Studies.

Dr. Karen Zulkowski

*Karen Zulkowski*  
(Signature)

4-8-04  
Date

Approved for the College of Nursing

Dr. Jean Ballantyne

*Jean Ballantyne PhD, RN*  
(Signature)

5-10-04  
Date

Approved for the College of Graduate Studies

Dr. Bruce R. McLeod

*Bruce R. McLeod*  
(Signature)

6-15-04  
Date

## STATEMENT OF PERMISSION TO USE

In presenting this thesis in partial fulfillment of the requirements for a master's degree at Montana State University, I agree that the Library shall make it available to borrowers under the rules of the Library.

If I have indicated my intention to copyright this thesis by including a copyright notice page, copying is allowable only for scholarly purposes, consistent with "fair use" as prescribed in the U.S. Copyright Law. Requests for permission for extended quotation from or reproduction of this thesis in whole or in parts may be granted only by the copyright holder.

Signature Shemi Nassar

Date June 8, 2004

## TABLE OF CONTENTS

1.INTRODUCTION .....	2
Problem .....	4
Purpose.....	4
Background .....	5
Conceptual Framework .....	8
Definitions.....	10
Assumptions.....	11
2.LITERATURE REVIEW .....	12
Heart Disease and Hormone Replacement Therapy.....	12
Breast Cancer and Hormone Replacement Therapy .....	15
The Women's Health Initiative .....	17
Women's Estrogen-Progestin Lipid-Lowering Hormone Atherosclerosis Regression Trial .....	21
The Women's Health Initiative Memory Study .....	21
The Million Women Study.....	22
Recommendations .....	23
Data on Prescribing Habits.....	25
Current Prescribing Data.....	27
Summary of Review of Literature.....	29
3.METHODS.....	31
Sample Population .....	31
Study Design .....	32
Instrument & Data Collection .....	32
Statistical Analysis .....	33
Human Subjects Approval .....	33
4.RESULTS.....	34
Years in Practice .....	39
Specialty Area .....	40
Gender.....	40
Professional Designation.....	41

## TABLE OF CONTENTS - CONTINUED

5. CONCLUSIONS .....	44
Future Implications & Research.....	47
Implications for Practice .....	48
Patient Education .....	48
Limitations .....	49
Summary .....	49
REFERENCES.....	51
APPENDICES .....	59
APPENDIX A .....	60
APPENDIX B .....	62

## LIST OF TABLES

Table	Page
1. Demographics.....	32
2. Current Reasons to Prescribe HRT.....	34
3. Past Reasons to Prescribe HRT.....	35

## LIST OF FIGURES

Figure	Page
1. Patient Questions About HRT.....	33
2. Current Recommendation on Length of HRT.....	35
3. Past Recommendation on Length of HRT.....	36
4. Gender Differences in HRT Prescribing.....	40
5. Alternatives to Hot Flashes by Professional Designation.....	41

## ABSTRACT

This study sought to examine the change in prescribing habits for hormone replacement therapy (HRT) in Montana practitioners since the publication of the Women's Health Initiative (WHI). **STUDY DESIGN:** A random sample of 160 Montana physicians, nurse practitioners, and physician assistants in the field of women's health were selected to receive a survey examining the effects of the WHI on their current and past prescribing habits. **RESULTS:** 53% of the sample returned the survey. Ninety-seven percent of the respondents were familiar with the WHI results, with 88% reporting that the results had a significant impact on their prescribing. Ninety-eight percent reported using HRT for menopausal symptoms, and only 4% currently use HRT for cardiovascular protection. This compares with 57% of respondents using HRT for cardiovascular protection prior to the WHI results. Ninety-four percent of the respondents report using other modalities for treating hot flashes and 96% use other modalities for osteoporosis treatment and prevention. Currently, most of the respondents are recommending that women use HRT for 1-5 years or for not set time. The results showed that the WHI had the most impact on those in practice greater than 10 years. Finally, there were very few differences in results when the data was analyzed based on specialty area, gender, or professional designation. **CONCLUSIONS:** This study demonstrated that the Women's Health Initiative results had a significant impact on participating Montana practitioners. It also showed that the providers in Montana are following national trends for HRT use and have quickly responded to new evidence in the women's health arena.

## CHAPTER 1

## INTRODUCTION

Hormone replacement therapy (HRT) is prescribed for approximately 50% of the postmenopausal women in the United States (Brett & Chong, 2001). However, use of HRT has been a controversial issue in women's health for years. The prototype hormone replacement therapy, Premarin® (0.625 mg of conjugated equine estrogen [CEE]), was approved for treating menopausal symptoms in 1942 by the Food and Drug Administration (FDA). The controversy surrounding HRT became prominent in the 1970's when data first emerged showing a strong relationship between continuous estrogen use and endometrial cancer. This link eventually led to combination estrogen/progestin formulations of HRT, such as Prempro® (0.625 mg CEE plus 2.5 mg of medroxyprogesterone acetate [MPA]). The purpose of the combination is to prevent proliferation of the uterine lining and virtually eliminate the risk of endometrial cancer.

Since Premarin's® original approval, many formulations of HRT have been approved by the FDA with similar indications: for the relief of vasomotor symptoms, vaginal atrophy, and the prevention of osteoporosis. The FDA required studies of short duration to prove efficacy for symptoms of menopause for the approval of Premarin®, Prempro®, and other similar products. Long-term health outcomes were not required and were not pursued. The use of HRT became controversial again when many practitioners began prescribing it as a panacea for preventing or treating chronic diseases in peri- and

postmenopausal women, such as osteoporosis and heart disease. These reasons are beyond the FDA approved indications.

Because there had been very few studies looking at the prospective effects of HRT, the National Institutes of Health designed the Women's Health Initiative (WHI) to prospectively examine, among many things, the effects of HRT, both estrogen alone and in combination with progestin, on chronic diseases in postmenopausal women. The study began in 1993 and was originally scheduled to publish results in 2005. However, the combination estrogen-progestin arm of the study was stopped early when data showed that HRT offered no cardioprotective benefit and increased a woman's chance of breast cancer (The Writing Group for the WHI, 2002). The WHI resulted in reports of providers changing their prescribing practices for HRT use, and in women voluntarily taking themselves off of HRT.

### Problem

Very little research has been conducted on the impact that the Women's Health Initiative results have had on the prescribing habits of physicians in regards to the continued use of HRT. The few studies and surveys conducted (Hersh, Stefanick, & Stafford, 2004; MedPanel, 2002) do show a decrease in prescriptions since the publication of WHI, but the research on changing physician behavior suggests that altering a long ingrained habit is not easy and often does not happen, even after repeated exposures to new information (Armstrong, Reyburn, & Jones, 1996; Sbarbaro, 2001; Sanders & Satyvavolu, 2002).

While physicians are surveyed frequently about changes in the health care arena, the

opinions and practices of nurse practitioners and physician assistants often go ignored. There are, in fact, no studies examining the prescribing habits of nurse practitioners and physician assistants in regards to HRT since the publication of the Women's Health Initiative.

#### Purpose

The purpose of this study is to compare and contrast the prescribing habits of Montana practitioners (physicians, nurse practitioners, and physician assistants) in regard to hormone replacement therapy use since the publication of the Women's Health Initiative.

#### Background

The average woman in the United States spends approximately 30 years in menopause with the probability for chronic disease development increasing with age. In fact, a menopausal woman has a 46% lifetime probability of developing heart disease, 20% for stroke, 15% for hip fracture, and 10% for breast cancer (Grady et al., 1992). Prior to the WHI, practitioners relied on data from observational or retrospective studies on HRT to guide them in prescribing HRT to protect the heart, prevent and treat osteoporosis, decrease wrinkles, protect against Alzheimer's, and reduce urinary incontinence.

It wasn't until the late 1990's that the publication of prospective, randomized studies called into question many of HRT's assumed benefits. Where HRT was once thought of as the gold standard for treatment and prevention for many of the above mentioned diseases for postmenopausal women, it quickly came under scrutiny in light of

prospective studies demonstrating no benefit for fracture protection in osteoporosis and no reduction in heart disease. One such study was the Postmenopausal Estrogen/Progestin Interventions trial, or PEPI Trial, which prospectively examined the effects of HRT on bone mineral density (BMD). While BMD increased at the spine and hip over 3 years in women taking estrogen replacement therapy (ERT) or various doses of combined HRT compared to women taking placebo, there were no significant reductions in fractures in the treatment group (The Writing Group for the Postmenopausal Estrogen/Progestin Interventions [PEPI] Trial, 1996). Other therapies, such as bisphosphonates and selective estrogen receptor modulators (SERMs), have shown significant fracture reduction in similar time frames (Cummings et al., 1999; Ettinger et al., 1999).

The Heart and Estrogen/Progestin Replacement Study, or HERS study, examined the effects of HRT on secondary prevention of heart disease in women with existing heart disease. The results of this study surprised researchers when no benefit was seen in reducing coronary heart disease events in women with heart disease who were taking Prempro®, the most commonly prescribed form of HRT (Hulley et al., 1998). This study led to the recommendation of not using HRT for heart protection, as had been previously assumed based on the simple tenet that replacing estrogen lost during menopause would place a woman at her pre-menopausal risk for heart disease. Additionally, although not a primary endpoint of the study, there was no significant difference in fractures rates in the HERS study when the treatment group was compared to placebo. This data, along with that from the PEPI Trial, may have fueled a 1999 decision by the Food and Drug Administration to revise the labeling for all forms of HRT to state that it is indicated for the

prevention and management of osteoporosis, but no longer indicated for the treatment of established osteoporosis as defined by World Health Organization (WHO) criteria.

The publication of PEPI and HERS profoundly challenged the accepted dogma of using HRT to treat and prevent chronic diseases in postmenopausal women. However, they were the only studies of their kind. The data would have to be replicated before practitioners would be willing to take millions of women off of HRT. Thus, practitioners eagerly awaited the results of the Women's Health Initiative (WHI) to guide their decision making. The WHI had two primary arms of the study: the first arm involving estrogen therapy alone for women who had undergone a hysterectomy, and the second arm involving combined estrogen and progestin for women with intact uteri. The primary outcome of WHI was the effect of HRT on coronary heart disease. Secondary outcomes included HRT's effect on osteoporosis and colon cancer, and the primary adverse outcome was invasive breast cancer.

In 2002, the combination estrogen/progestin arm of the study was stopped early due to results that combined HRT-users experienced an increase in breast cancer risk. As data was analyzed and published, the results verified the outcome of the HERS study in regard to a lack of cardioprotective benefit of HRT. This led many to question the use of routinely prescribing HRT for postmenopausal women for any chronic disease prevention. As more data was released, the confusion escalated and the controversy spiked again. If physicians weren't taking patients off of hormone therapy, then patients were doing so voluntarily based on the fear created by media attention.

Patients and clinicians may be drawn to alternative modalities for the treatment of

hot flashes in light of the WHI results. Some alternatives include antidepressants, antihypertensives, and herbal therapies. One of the more commonly used herbal therapies is black cohosh. The data showing black cohosh's effectiveness is variable. This is probably due to the many different study designs lacking scientific rigor. Many studies showing a decrease in the number of hot flashes with black cohosh were poorly designed or were not placebo controlled. According to the North American Menopause Society (NAMS), 2 out of 3 placebo-controlled trials showed that black cohosh did not have a significant effect on reducing the number of hot flashes compared to placebo in postmenopausal women (The North American Menopause Society [NAMS], 2004). The third placebo-controlled trial did show that black cohosh decreased hot flashes when compared to both ERT and placebo. Another study assessing hot flashes in breast cancer survivors showed no difference in outcomes between black cohosh and placebo (Jacobson et al., 2001). Currently, the National Center for Complimentary and Alternative Medicine is in the recruitment phase of a prospective, placebo-controlled trial to assess black cohosh's effectiveness in treating hot flashes (National Institutes of Health [NIH], 2004).

Another popular choice for hot flash treatment is clonidine, an alpha 2 agonist used in treating hypertension. Data supporting clonidine's effectiveness in treating hot flashes dates back over 20 years. In 1982, Laufer et al showed a significant decrease in hot flashes compared to baseline and placebo. In 1987, Nagamani, Kelder and Smith published results showing a significant decrease in the number of hot flashes, as well as severity and duration of hot flashes, with 8 weeks of clonidine treatment with minimal side effects and essentially no change in blood pressure or pulse. More evidence for clonidine's effectiveness for hot

flash treatment was reported by Freedman and Dinsay (2000) who determined that clonidine increased the sweating threshold in symptomatic, menopausal women. Selective serotonin re-uptake inhibitors (SSRI), the newest class of antidepressants, may work in a similar fashion to treat hot flashes. SSRI's alter the serotonin and/or norepinephrine concentrations in the brain, and serotonin has been shown to widen the thermoneutral zone in rats (NAMS, 2004).

### Conceptual Framework

The conceptual framework used for assessing clinician prescription behavior change is based on the Transtheoretical Model of Change. This theory has demonstrated the ability to explain behavior change across a broad range of behaviors, from organizational change to treatment for addiction (Prochaska, Prochaska, & Levesque, 2001). The Transtheoretical Model integrates a number of theoretical concepts of change, including stages of change, decisional balance, and processes of change (Prochaska, Prochaska, & Levesque, 2001).

There are five *Stages of Change* that an individual goes through when modifying their behavior: (1) Precontemplation- no intention of changing a particular behavior; (2) Contemplation - thinking about making a behavior change; (3) Preparation - making plans for change; (4) Action - implementing plans for change; and (5) Maintenance - sustaining changes for six months or more (Prochaska, Prochaska, & Levesque, 2001).

The second concept in the Transtheoretical Model is *Decisional Balance*, which involves assessing the pros and cons of change. The balance of pros and cons is related to

the stage of change of an individual, with cons outweighing pros in the Precontemplation Stage and pros outweighing cons in the Action Stage (Prochaska, Prochaska, & Levesque, 2001).

The final concept in the Transtheoretical Model is the *Processes of Change*. There are ten fundamental processes that can be elicited to change behavior. Consciousness Raising, Dramatic Relief and Environmental Reevaluation are emphasized in the Precontemplation Stage. Self-Reevaluation is utilized in the Contemplation Stage and Self-Liberation is used in the Preparation Stage. Contingency Management, Helping Relationship, Counter-Conditioning, and Stimulus Control are all processes used in both the Action and Maintenance Stages of Change (Prochaska, Prochaska, & Levesque, 2001).

Behavior change is a continuous process (Cohen, Halvorson, & Gosselink, 1994). The Transtheoretical Model of Change implies that the success of an intervention depends upon the nature of the intervention itself and the amount of "readiness" of the respondent (Cohen, Halvorson, & Gosselink, 1994). Physician behavior is likely to change only when physicians have a compelling need (at or beyond the contemplation level) to change their practice and when they have information about how to make the desired changes (Cohen, Halvorson, & Gosselink, 1994).

This study will demonstrate where Montana practitioners lie on the change continuum. The survey results will show whether the data from the WHI is compelling enough to change established prescribing habits related to HRT and the treatment and prevention of chronic disease in postmenopausal women.

### Definitions

The American College of Obstetrics and Gynecologists (ACOG) and NAMS have recommended using "uniform and consistent" terminology to describe hormone therapies offered to women at menopause. For example, NAMS recommends the following terminology:

ET - estrogen therapy

EPT - combined estrogen and progesterone therapy

HT - hormone therapy that encompasses both ET and EPT

Local ET - preparations of ET that have predominately vaginal, not systemic effects

Progestogen - encompassing both progesterone and progestin

However, due to the pervasiveness of "old" terminology in the literature, the following terms will be used for the purposes of this paper:

- **HRT** - hormone replacement therapy - a generic term to describe a combination of estrogen and progestogen therapy in women. The most commonly prescribed combination preparation, and the one studied in the HERS and WHI studies, is Prempro®, or 0.625 mg/day conjugated equine estrogen and medroxyprogesterone acetate 2.5 mg/day. There are many other formulations of HRT that include different doses of both estrogen and progestogen, different types of estrogen and progestogen, as well as different delivery systems, such as a transdermal patch, a pill, and creams.
- **ERT** - estrogen replacement therapy- defined as an estrogen only preparation, most often used in women who have had a hysterectomy and are no longer at risk for uterine hyperplasia and/or cancer related to unopposed estrogen.
- **Current Use** - prescribing behavior of hormone therapy since the publication of the WHI study.
- **Past Use**- prescribing behavior of hormone therapy prior to the publication of the WHI study.

Assumptions

“Assumptions refer to those concepts and ideas that the investigator accepts as valid and salient to the study, “ (Butterfield, Lindeman, Valanis, & Spencer, 1995). This study was conducted under the following assumptions: 1) that data on physician prescribing behavior and habits also applies to nurse practitioners and physician assistants in the absence of literature addressing the habits of the latter two practitioners; 2) that the majority of practitioners in the women’s health arena were aware of the WHI study to some degree; and 3) that in Montana, the prescribing patterns of HRT follow the national trend as one of the top 10 most prescribed medications.

## CHAPTER 2

### LITERATURE REVIEW

#### Heart Disease and Hormone Replacement Therapy

The assumed benefits of hormone replacement therapy (HRT) were largely based on observational studies. One of the more widely held beliefs was that HRT was beneficial in preventing heart disease in women (Stampfer & Colditz, 1991; Grady et al., 1992; Rijpkema, van der Sanden, & Ruijs, 1990). This belief was based on the observation that the incidence of heart disease in women drastically increased after menopause, and that women taking HRT showed a lower incidence of heart disease compared those who were not taking HRT. This assumption was based on data from cohort and case/control studies (Henderson, 1985). Cutler and Garcia (1984) cited lower cholesterol levels in women using estrogen alone or combined HRT. Specifically, Cutler and Garcia noted that estrogen replacement therapy (ERT) significantly increased high-density lipoprotein (HDL), a marker accepted as cardioprotective (1984). They cited multiple studies showing a decrease in myocardial infarctions, ischemic heart disease, and death related to heart disease in women taking HRT compared to non-users (Cutler & Garcia, 1984) leading them to conclude that HRT had a "relative protective effect" for postmenopausal women.

A recent cohort study is the Nurse's Health Study. Results published in 1995 showed that postmenopausal women on HRT had half the incidence of heart disease than women who did not use hormones. This reinforced the belief that replacing missing

hormones brings a woman back to her pre-menopausal state and thus, her pre-menopausal risk of heart disease (Grodstein, Manson & Stampfer, 2001). On the other hand, results showed that after 10 years of ERT use, the risk of breast cancer increased significantly, and adding progesterone further increased that risk (Colditz & Rosner, 2000). However, these observations may have demonstrated selection bias. HRT users tend to be more affluent, leaner, more educated, exercise more and drink alcohol more - factors which are associated with an increased risk of breast cancer and a decreased risk of cardiovascular disease (Nelson, Humphrey, Nygren, Teutsch & Allen, 2002). Women who use HRT generally have access to health care, are more likely to be treated for comorbid conditions, and can afford to fill their prescriptions (Nelson, Humphrey, LeBlanc, et al., 2002). Additionally, "long-term users of HRT are treatment-compliant, itself a factor associated with better health," (Nelson, Humphrey, LeBlanc, et al., 2002, p. 14).

One of the first randomized, prospective, double-blind trials on the effects of HRT was the Postmenopausal Estrogen Progestin Intervention (PEPI) Trial. The PEPI trial sought to examine whether HRT would reduce risk factors for heart disease and osteoporosis. The data for osteoporosis showed that while bone mineral density (BMD) increased at the spine and hip over 3 years in women taking ERT or various doses of combined HRT compared to women taking placebo, there were no significant reductions in fractures in the treatment group (The Writing Group for the Postmenopausal Estrogen/Progestin Interventions [PEPI] Trial, 1996). In regards to heart disease, the results showed a significant increase in high-density lipoproteins (HDL) and a significant decrease in low-density lipoproteins (LDL) in women taking estrogen or

estrogen/progestin preparations compared to women taking a placebo pill (The Postmenopausal Estrogen/Progestin Interventions [PEPI] Trial Investigators, 1995). Additionally, those taking placebo had an increase in mean fibrinogen, another risk factor for heart disease, compared to those taking HRT (The PEPI Trial Investigators, 1995). Because of the positive influence on HDL, LDL, and fibrinogen, all surrogate markers for heart disease, HRT was believed to be cardioprotective.

This belief pursued despite the publication of a second prospective, randomized, placebo-controlled study. The Heart and Estrogen/Progestin Replacement (HERS) study examined the effects of HRT on secondary prevention of heart disease in women with existing heart disease. The results of this study demonstrated no benefit in reducing coronary heart disease events in women with heart disease who were taking Premarin®, the most commonly prescribed formulation of HRT, compared to women taking placebo (Hulley et al., 1998). The authors of this study recommended against initiating HRT for secondary prevention of heart disease.

Despite this evidence, many practitioners continued to believe in the inherent benefit of HRT to overall cardiovascular health. The North American Menopause Society (NAMS) and the American College of Obstetricians and Gynecologists (ACOG) continued to recommend long term HRT use for primary prevention of heart disease contingent upon results from the Women's Health Initiative (WHI), which were not expected until 2005. In 2000, NAMS published a decision tree for the use of hormone replacement therapy in postmenopausal women. At that time, the consensus opinion of NAMS included the long-term use of HRT (possibly lifelong) to treat menopausal symptoms, reduce the risk of

coronary heart disease (CHD), and to reduce the risk of osteoporosis (The North American Menopause Society [NAMS], 2000). Specifically, "the goal of ERT/HRT is to enhance quality of life as well as to reduce death and disability from coronary heart disease and osteoporosis," (NAMS, 2000, p.77 ).

### Breast Cancer and Hormone Replacement Therapy

Because of the assumed benefit to a woman's heart, the possible risk of breast cancer risk had not prevented practitioners from prescribing HRT. The breast cancer issue is confusing and the media attention surrounding HRT use and breast cancer incidence has been intense. Many studies have reported that with longer use of HRT, there is a greater risk of breast cancer (Beral, Banks, Reeves & Appleby, 1999; Colditz, 1999; Marsden, 2002). Weiss et al. (2002) reported increased risk of breast cancer with HRT use of 5 years or more, with the risk dissipating after discontinuation of use. Marsden (2000) echoed these results stating that breast cancer risk falls after cessation of use, suggesting that HRT has a tumor growth promoting effect. Marsden (2000) goes further to state that HRT promotes the growth of pre-existing breast cancer rather than initiating a malignancy. Still, other authors reported no increased risk of breast cancer with HRT use (Lando, 1999).

Despite the possible increased risk of breast cancer with HRT use, outcome results have been conflicting. Many studies have shown that the overall mortality resulting from breast cancer was lower in HRT users (Nanda et al., 1999; Jernstrom, Frenander, Ferno & Olsson, 1999). Researchers debate whether this phenomenon is due to the biologic activity

of hormones or to earlier detection of breast cancer due to frequent follow-up of patients on HRT (Schairer et al., 1999; Gajdos, Tartter, & Babinszki, 2000). Some researchers concluded that breast cancers are less aggressive in HRT users (Beral, Banks, Reeves & Appleby, 1999; Cheek et al., 2002). Still more confusing were data showing no adverse outcomes with HRT use in breast cancer survivors (DiSaia, Brewster, Ziogas, & Anton-Culver, 2000) and no increased recurrence and lower mortality in breast cancer survivors who used HRT (Meurer & Lena, 2002; O'Meara, Rossing, Daling, Elmore & Barlow, 2001; Natrajan & Gambrell, 2002; Marsden, 2002).

In the end, despite a patient's potential fears of breast cancer, practitioners continued to rely on recommendations stating that the long term benefits of HRT outweighed any possible increase in risks to direct their prescribing. The recommendations began to change with the early publication of results from the Women's Health Initiative.

### The Women's Health Initiative

The Women's Health Initiative (WHI) was a large scale, prospective study sponsored by the National Institutes of Health (NIH) to examine "the most common causes of death, disability and poor quality of life in postmenopausal women – cardiovascular disease, cancer, and osteoporosis" (NIH, 2003). Four years after the data from HERS was published, the combined estrogen-progestin arm of the WHI was stopped early due to increased risks associated with combined HRT.

A major area of study in the WHI was the use of hormones and the prevention of chronic diseases. Two separate arms with similar study endpoints were designed: one

studying the effects of combined estrogen and progestin (i.e. Prempro®) and one studying the effects of estrogen replacement alone (i.e. Premarin®). The primary outcome in both arms of the studies was the effect of HRT on coronary heart disease, with a secondary outcome being the effect on hip fracture incidence. Invasive breast cancer was the primary adverse outcome. The study that examined the outcomes of combined HRT enrolled predominately healthy postmenopausal women who had a uterus. The average age of enrolled patients was 63. This arm of the WHI study was originally intended to last eight years. However, the study was stopped early (at 5.2 years) when the Data and Safety Monitoring Board determined that the health risks of HRT outweighed the potential benefits. Specifically, the authors concluded that “the evidence for breast cancer harm, along with evidence for some increase in CHD, stroke and PE [pulmonary embolism], outweighed the evidence of benefit for fractures and possible benefit for colon cancer...,” (The Writing Group for the Women’s Health Initiative [WHI] Investigators, 2002, p.325). The results of the study showed a 26% increase in invasive breast cancer (HR 1.26 [1.00-1.59]), a 29% increase for CHD events (HR 1.29 [95% CI 1.02-1.63]), and a 41% increase in strokes (HR 1.41 [95% CI 1.07-1.85]) for women taking HRT compared to women taking placebo (The Writing Group for the WHI Investigators, 2002). The results also showed an increase in breast cancer risk over time. The benefits of HRT use included a decrease in colorectal cancer (HR 0.63 [95% CI 0.43-0.92]) and a decrease in hip fractures (HR 0.66 [95% CI 0.45-0.98]). There was no difference in overall mortality or cause of death (The Writing Group for the WHI Investigators, 2002).

A 2002 scientific review of literature conducted by Nelson, Humphrey, Nygren,

Teutsch, and Allen echoed the WHI study results: HRT essentially offers no cardiovascular protection, significantly increases the risk of stroke, thromboembolism and pulmonary embolism, increases BMD and decreases fracture risk, increases breast cancer risk with no change in mortality, and decreases the risk of colon cancer. A Danish study found that HRT, consisting of estrogen combined with a different formulation of progestogen than that used in WHI, increased the incidence of both ischemic and hemorrhagic stroke only in hypertensive women. Normotensive women taking HRT had no increased risk for stroke (Lokkegaard, Jovanovic, Heitmann, et al., 2003).

The results of the Women's Health Initiative drew intense media attention causing millions of women to abruptly stop taking their HRT. There was also confusion among clinicians on how to interpret the results of the study. As stated previously, the average age of women in the study was 63; the average age of a woman going through menopause in the United States is 51 (Millonig, 1996). This led many researchers and clinicians to question whether these results could be extrapolated to younger menopausal women. Also, women with severe menopausal symptoms were excluded from the WHI study as it was not designed to study quality of life issues at menopause, such as vasomotor symptoms. Additionally, only one drug regimen was tested - 0.625 mg/d conjugated equine estrogen plus 2.5 mg/d medroxyprogesterone acetate. Thus, common critiques of this arm of the WHI include the fact that the women studied started taking HRT later than one would expect, which does not reflect traditional use, and the fact that only one formulation was studied (Lemay, 2002).

While the relative risk increases sound impressive, the absolute risks of HRT use

are low. Over one year, 10,000 women taking HRT might experience 7 more CHD events, 8 more strokes, 8 more pulmonary embolisms, 8 more breast cancers, 6 fewer colorectal cancers, and 5 fewer hip fractures compared to women not using HRT (The Writing Group for the WHI Investigators, 2002). Still, the authors of the WHI concluded that HRT should not be prescribed for primary prevention of chronic diseases for healthy women.

A second analysis on heart disease from the Women's Health Initiative examined data from the final endpoint of the study which was July 2002. The authors, who focused solely on the impact of HRT on heart disease, concluded that HRT offers no cardioprotection for healthy postmenopausal women, and HRT may even increase their risk of coronary heart disease (Manson et al., 2003). Of note, neither aspirin therapy or statin therapy (a category of prescription drugs used to lower cholesterol) modulated the risk of HRT therapy (Manson et al., 2003).

In March 2004, the NIH stopped the estrogen-only arm of the WHI study which included over 11,000 women who had undergone hysterectomies. Women in this arm of the study were followed for approximately 7 out of the planned 8 years. This study was stopped one year early because researchers felt enough data had been collected. Preliminary results suggest that estrogen alone has neither a positive or a negative effect on heart disease (the primary endpoint of the study), an increased risk of stroke, and a decreased risk of hip fracture. But, estrogen alone did not increase the risk of breast cancer (National Heart, Lung, and Blood Institute [NHLBI], 2004). These results are tied to the same criticisms of the WHI arm using combined estrogen and progestin, as the participants for both arms of the study were recruited at the same time. According to the

U.S. Food & Drug Administration (FDA) website, “the increased risk of stroke with estrogen alone outweighs any benefits found in the study,” particularly in a study population of healthy women (2004). The final publication of the estrogen-only arm of the WHI study in a peer reviewed journal is not expected until at least May 2004.

#### Women’s Estrogen-Progestin Lipid-Lowering Hormone Atherosclerosis Regression Trial

The WELLHART (Women’s Estrogen-Progestin Lipid-Lowering Hormone Atherosclerosis Regression Trial) Study prospectively examined the ability of HRT to slow the progression of atherosclerosis in postmenopausal women with a coronary artery lesion. This study examined different formulations of HRT than was used in the WHI and the HERS studies. The authors of this study (Hodis et al., 2003) concluded that estrogen alone or in combination with progestin had no effect on the progression of atherosclerosis. This study also allowed patients to take statin drugs to lower cholesterol. To add support to the conclusion that HRT confers no cardioprotective benefit, Grady et al.(2002) published results from an extension of the HERS trial, HERS II, which showed that HRT offers no cardiovascular benefit over 6 years of follow up in women with coronary heart disease.

#### The Women’s Health Initiative Memory Study

The Women’s Health Initiative Memory Study (WHIMS) was designed to assess the effect of HRT on cognition. The arm of WHIMS studying combined HRT was stopped

early in March of 2003. Shumaker et al (2003) reported that more women 65 years or older in the estrogen/progestin group had significant cognitive decline on the Modified Mini-Mental State Examination compared with the placebo group. This study also found an increased risk of stroke in those taking combination HRT compared to a placebo group, regardless of age (Shumaker et al., 2003). The authors concluded that combination HRT should not be recommended for the prevention of Alzheimer's disease. Similar conclusions were made by Beral, Banks, and Reeves (2002) after they noted that the randomized trials to date suggest that HRT does not improve cognitive function or slow the progression of Alzheimer's disease. The estrogen-only arm of WHIMS was also stopped early due to results showing a trend toward increased risk in "probable" dementia and/or memory impairment in women who took estrogen alone (U.S. Food & Drug Administration [FDA], 2004).

#### The Million Women Study

New data published in 2003 from the Million Women study corroborated the breast cancer risk results from the WHI. The primary purpose of the Million Women study was to determine the mortality rate from breast cancer and the use of HRT. Many formulations of HRT were assessed, along with many different doses and routes of administration. Of the 1,084,110 postmenopausal women recruited in the study, over 800,000 women were included in the data analysis. The results indicated that the risk of breast cancer was significantly higher in ever-users of HRT than never-users (Million Women Study Collaborators, 2003). Past users were at no increased risk of breast cancer regardless of

how long it had been since they ceased using HRT, except those stopping within the previous year. These women had a slightly increased relative risk of breast cancer (Million Women Study Collaborators, 2003). The authors also concluded that combined HRT poses the greatest increase in risk, and estrogen alone, regardless of dose, formulation or route of administration, also increased risk but not to same degree as combination use (Million Women Study Collaborators, 2003). The relative risk of breast cancer increased as duration of use increased. The authors determined that current users of HRT have a 22% higher mortality rate related to breast cancer (Million Women Study Collaborators, 2003), however the absolute numbers are small. Interestingly, they found no increase in relative risk of breast cancer in past users of HRT, stating that "...use of HRT on the risk of breast cancer wore off largely, if not wholly, within 5 years of ceasing use of HRT," (Million Women Study Collaborators, 2003, p. 427).

### Recommendations

The appropriate use, duration, and formulation of hormone replacement therapy has become obscure, particularly since the publication of the Women's Health Initiative. Since the publication of WHI, the North American Menopause Society has amended their recommendations twice, first in October of 2002 and again in September of 2003. The latest consensus opinion from NAMS includes the following: 1) the primary indication for HRT is to treat severe menopausal symptoms; 2) topical estrogen is recommended for the treatment of vulvar or vaginal atrophy if that is the only complaint; 3) HRT should not be used for the primary or secondary prevention of CHD or stroke; 4) both estrogen

replacement and combined HRT increase the risk of breast cancer with use longer than 5 years; and 5) if a woman requires therapy for osteoporosis other medications should be considered (2003). Because studies have shown nearly equal amounts of vasomotor symptom relief, vulvovaginal relief, and preservation of bone mineral density with lower doses of HRT, lower doses of HRT should be considered to treat menopausal symptoms (NAMS, 2003). NAMS was unable to define a safe window for HRT use and generally recommends using the lowest dose of HRT for the shortest amount of time (2003). NAMS (2003) does concede that there may be situations where long term use of HRT is necessary, such as symptom relief after failure to withdraw from HRT, or where alternative therapies for osteoporosis are contraindicated for women at high risk. In these rare situations, the patient must be made aware of the risks involved and be under strict clinical supervision (NAMS, 2003). Finally, NAMS recognizes that the absolute risks and benefits of HRT are small (2003).

The U.S. Preventive Services Task Force (USPSTF) “recommends against the use of estrogen and progestin for the prevention of chronic conditions in postmenopausal women,”(U.S. Preventive Services Task Force [USPSTF], 2002). Although they did not examine the use of HRT for menopausal symptoms, the USPSTF recommends that women be informed of increased risk of CHD, stroke and thromboembolism within the first 1-2 years of therapy (USPSTF, 2002). They specifically recommend using other medications for the prevention and treatment of osteoporosis and do not recommend using HRT for the prevention of CHD (USPSTF, 2002).

Finally, the recommendations of the American College of Obstetricians and

Gynecologists (ACOG) are similar. In terms of short-term use of HRT, ACOG does recommend the use of HRT for the relief of menopausal symptoms since the benefits are likely to outweigh the risks (American College of Obstetricians and Gynecologists [ACOG], 2002). ACOG does stress that HRT use for the relief of menopausal symptoms is a individualized decision, and each woman should consult with her physician to discuss her individual risks and benefits associated with HRT (2002).

Certainly, data on the use of HRT and the long term health outcomes of its use will continue to be pursued. For one, the second arm of the WHI which is studying the use of estrogen alone has just been completed. The mere fact that this arm continued nearly two years longer than the combination HRT arm raises many questions about the role of progestin in chronic diseases of postmenopausal women. It appears that the safest recommendation for combined HRT use may be: the lowest possible dose for the shortest amount of time.

Given all the new data on HRT and it's controversial history, will practitioners even change their prescribing habits? Many authors stand firm and still recommended HRT as the best treatment and consider it safe for treatment of menopausal symptoms (Grimes & Lobo, 2002; Lemay, 2002).

#### Data on Prescribing Habits

Multiple research articles refer to particular prescribing habits of physicians, however research on changing prescribing behavior is limited. There are no studies referring to changing prescribing habits of either nurse practitioners or physician's

assistants. The research that has been done on physicians suggest that changing physician prescribing behavior is quite difficult.

Sbarbaro (2001) studied different avenues to change physicians prescribing behavior. He found that continuing medical education lectures do not alter prescribing habits, even when practice guidelines are clear and supported by strong evidence (Sbarbaro, 2001). Prescribing behavior is more likely to change when new information is endorsed by local or national opinion leaders, delivered in an interactive format, or when a physician is compared to peers and national standards (Sbarbaro, 2001).

Research conducted by Armstrong, Reyburn, and Jones (1996) showed similar results. They found that traditional avenues for change, such as clinical meetings and journals articles, cannot bring about large scale change in prescribing habits. Most changes occurred because the practitioner was challenged or surprised, was prepared to change, through accumulation of evidence and experience, or due to patient feedback (Armstrong, Reyburn, & Jones, 1996).

Other authors found that direct feedback of prescribing practices and reminders at the time of prescribing appear to impact prescribing practices (Ahluwalia, Weisenberger, Bernard, & McNagny, 1996). However, one study demonstrated that a "highly visible" chart reminder did not motivate physicians to comply with established clinical guidelines to aggressively treat hypertension in high-risk patients (Sanders & Satyvavolu, 2002).

The effect of drug samples and the cost of prescription medicines on the prescribing habits of physicians has also been investigated. Boltri, Gordon, and Vogel (2002) examined the compliance rate of prescribing first-line drug therapies for hypertension

before and after drug samples were allowed in the Medical Center of Central Georgia. The authors found that there was a significant increase in first-line therapies prescribed for hypertension when samples were prohibited. Reichert, Simon and Halm (2000) assessed the relationship between the cost of medications and physician prescribing. They found that while a large majority of doctors felt that the cost of medicines was an important consideration in their decision to prescribe, an equally large amount did not accurately know the cost of the medicines they prescribed, and only a small percentage had access to drug cost data. Without accurate information, it is unlikely that the cost of a medicine will impact prescription habits (Reichert, Simon & Halm, 2000).

It may be that the area of specialization providers practice in affects the speed at which they change their practice. O'Connor (2002) found that specialists in a given field tend to adopt changes faster than primary care physicians. For example, gastroenterologists initiated triple antibiotic therapy for the treatment of *H. pylori* nearly two years before primary care physicians, despite the publication of consensus guidelines. O'Connor concluded that recommendations to eliminate an established clinical behavior may be more difficult to follow than recommendations calling for a new behavior (2002).

#### Current Prescribing Data

Data on the effects of the Women's Health Initiative on HRT prescriptions is beginning to emerge. MedPanel (2002), a medical research and communications firm, released results from an online survey regarding HRT and physician prescribing. The

results indicated that physicians were “drastically changing prescription habits” based on patient concerns and the latest information, with 90% of the physicians surveyed citing the WHI study as a major influencing factor (MedPanel, 2002). Only 6% of the respondents stated that they would continue to prescribe HRT as they have in the past, while 80% said they will continue to recommend HRT for disabling vasomotor symptoms (MedPanel, 2002). The survey indicated a reduction in the amount of HRT prescriptions from 52% in 2001 to 12% in 2002 (MedPanel, 2002). The physicians also reported a significant increase in patient discussions regarding “natural alternatives” to HRT.

Two recent studies examined the change in HRT prescriptions since the publication of the WHI study. The first study, published by Hersh, Stefanick, and Stafford (2004), showed a decrease in the use of HRT after both the WHI study and the follow-up HERS study, HERS II. Prescriptions declined immediately following the publication of both studies in July 2002, with subsequent declines in the months following. The decrease in prescriptions was mostly noted in oral preparations of HRT or ERT, with Prempro® and Premarin® accounting for 80% of the decline (Hersh, Stefanick, and Stafford, 2004). The authors cite the “media cascade” after the publication of the WHI and HERS II studies as enhancing information dissemination, and concluded that physicians responded rapidly to clinical evidence and revised guidelines (Hersh, Stefanick, and Stafford, 2004).

Another study by Blümel et al. (2004) showed similar results. They found that prescriptions for HRT dropped in the three months following the WHI study, with the most significant decline occurring in the oral preparations of combination HRT. Over 64% of the physicians surveyed reported changing their approach to HRT, with the main changes

consisting of a more thorough risk/benefit assessment of HRT, using lower doses of HRT, recommending a shorter duration of therapy, and switching to transdermal preparations (Blümel et al., 2004).

### Summary of Review of Literature

Despite observational evidence suggesting a cardioprotective benefit with HRT use, recent prospective studies have proven otherwise. Many prospective, randomized, placebo-controlled studies have shown that HRT, either alone or in combination, does not guard against heart disease, and may increase the risk of breast cancer, stroke and dementia. These studies show that HRT may be beneficial in reducing colon cancer and osteoporosis fractures, however the risks of HRT use outweigh the benefits.

Recommendations from leaders in women's health have been amended since the publication of the WHI and other similar studies. HRT is no longer recommended as lifelong therapy for the treatment or prevention of chronic diseases. Specifically, HRT is not recommended for the primary or secondary prevention of heart disease. HRT is currently recommended only for the short term treatment of menopausal symptoms at the lowest dose possible. Clinicians are encouraged to counsel patients about their individual risks and benefits associated with HRT use.

Existing research on prescribing habits suggest that long-standing habits often do not change even with clear guidelines and compelling evidence. Some practitioners may change their prescribing due to their experience with a particular drug, their readiness to change, or patient feedback. Specialists in a given area may be more willing to change their

habits than primary care physicians. Despite these facts, current prescribing data does show a decrease in HRT prescriptions following the publication of the WHI. Current studies are suggesting that practitioners are rapidly changing their prescribing habits in conjunction with revised guidelines and clinical evidence.

## CHAPTER 3

## METHODS

This study was designed to examine the prescribing habits of Montana practitioners with regard to hormone replacement therapy (HRT), and the effects of the Women's Health Initiative (WHI) on those prescribing habits. A descriptive study design was chosen to assess all types of practitioners (physicians, nurse practitioners, and physician assistants) in Montana concerned with women's health.

Sample Population

A random sample of 160 medical doctors (MD), doctors of osteopathy (DO), nurse practitioners (NP), and physician assistants (PA) from the state of Montana were selected to receive a survey on prescribing habits for HRT. Health care specialties which were most likely to treat women as they went through menopause were selected, including Obstetrics and Gynecology (OB/GYN), Family Practice (FP), General Practice (GP), and Internal Medicine (IM). The number of physicians (both MD's and DO's) in Montana within these groups was estimated at 1000 based on the 2003 Montana Medical Association Directory of Montana Physicians. The author also estimated the number of NP's and PA's practicing in Montana to be around 300 for each group. Surveys were sent to a random sample of 10% of the selected physicians specialists, nurse practitioners, and physician assistants, for total of 160 mailed surveys.













































































