The efficacy of *Dioscorea villosa* cream in the treatment of menopausal syndrome

By

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I, Louise Macquet-Maurel, do declare that this dissertation is representative of my own work, both in conception and execution.

Signature of student 1/08/2003 **Date of signature**

Approved for final submission

Signature of supervisor 1/8/2003 **Date of signature**
Dr D.F Naudé M.Tech:Hom (T.N)

I would like to dedicate this dissertation to my parents; Bert and Sue Macquet-Maurel, to my sisters; Amanda and Jennifer Macquet-Maurel, and to my partner David Ardé; for their continued love, support and encouragement throughout my life.

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ABSTRACT

The purpose of this randomised double-blind placebo-controlled study was to evaluate the efficacy of *Dioscorea villosa* cream in the treatment of menopausal syndrome in terms of subjective and objective data; and to compare the subjective data with that obtained from a concurrent study of ProgestoNat® cream (McTeer, 2003).

Thirty female subjects were selected to participate in this study. They were randomly divided into two equal groups of fifteen subjects each. Group 1 was the Treatment group, receiving *Dioscorea villosa* cream, and Group 2 was the Placebo group. The placebo cream given to group 2 was indistinguishable from the experimental cream. It contained the identical combination of ingredients with exception to that of *Dioscorea villosa* (see Appendix C). The data gained from the patients in the placebo group (group 2) were shared with a concurrent study of similar methodology (The efficacy of *ProgestoNat* ® cream in the treatment of menopausal syndrome, McTeer, 2003) and vice versa. This was possible, as the placebo applications used in the two studies were identical in terms of ingredients, appearance, dosage and posology. The subjective and objective measurements in the two studies were also identical.

Subjects were required to attend three consultations with the researcher. During all three consultations the Greene Climacteric Scale Questionnaire was completed in order to assess the severity of the symptoms experienced by the participants. During the first and third consultations a blood sample was drawn from each participant for the measurement of progesterone levels. Subjects were given a container of either *Dioscorea villosa* or placebo cream, according to their allocated group. A metered dose (20 mg) (one pump action) of the cream was applied every night, on a rotational basis to the face, neck, upper chest, breasts, inner arms and thighs, palms of hands and soles of feet.

Statistical analyses were performed using non-parametric tests. Inter group analysis (treatment versus placebo) revealed that the differences between the two groups in terms of subjective and objective data were insignificant.

Within the treatment group a significant improvement was observed between the first and third consultations for the depression symptom scores. Anxiety symptom scores improved significantly between the first and second consultations as well as between the first and third consultations. There was also a significant improvement in somatic symptom scores between the first and second as well as between the first and third consultations. Sexual symptom scores improved significantly between the first and third consultations. There was a significant difference between the two progesterone measurements in the treatment group. However, this improvement was in the reverse direction to that

which was expected. The progesterone measurements decreased as opposed to the expected increase.

Within the placebo group there was a significant improvement between the first and third consultations for the depression symptom scores. Anxiety and somatic symptom scores improved significantly between the first and second as well as between the first and third consultations. The difference between the progesterone measurements for the placebo group was not significant.

Comparisons of the subjective data between group 1 (*Dioscorea villosa*), group 2 (placebo) and group 3 (ProgestoNat ®) revealed that the differences were insignificant.

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CHAPTER 1

1.1 INTRODUCTION

The current medical view of menopause is of a deficiency disease rather than a normal physiological process. Menopause is much more than simply a biological event. Social and cultural factors contribute greatly to how women react to menopause. Modern society has placed great value on the allure of everlasting youth, resulting in a cultural devaluing of older women. This is the root of the negativity associated with achieving menopause (Pizzorno & Murray, 1999).

Hormone Replacement Therapy (HRT) is the most frequently employed method of relieving the symptoms and preventing the complications associated with menopause. However, HRT is associated with many side effects, including breast cancer, endometrial cancer and thromboembolic disease. HRT is not a suitable treatment for many women as it has many contraindications (Dreyer, 1999). The risks and benefits should be considered for each individual before the decision is made to commence HRT (Panidis et al. 2001).

Many women are now seeking alternatives to hormonal therapies for the management of menopausal symptoms. Among the alternative treatments available is Natural progesterone cream. Natural progesterone refers to the progesterone that has the identical chemical structure to the progesterone made in the body. It is produced *in vitro* from *Diosgenin*, a steroid-like substance extracted from Mexican wild yam (*Dioscorea villosa*). *Dioscorea villosa* is not

used in its naturally occurring form as it is not known whether the human body is able to make the conversion of *Diosgenin* into a form of progesterone that may be utilised by the body (Bond & Rushton, 1999). There have been no studies as to the safety or efficacy of wild yam in the management of menopausal symptoms. A study was performed by Komesaroff et al. (2001) on the effects of wild yam extract on menopausal symptoms, lipids and sex hormones. The study was conducted on women whose average time since last menstrual period was 4.3 to approximately 0.9 years. These women were therefore classed as postmenopausal. No studies have been performed to date on the effects of *Dioscorea villosa* mother tincture (in its naturally occurring form) on menopausal symptoms in perimenopausal women.

1.2 OBJECTIVES

1.2.1 First objective

The first objective is to determine the efficacy of *Dioscorea villosa* cream in the treatment of menopausal syndrome in terms of subjective data.

1.2.2 Second objective

The second objective is to determine the efficacy of *Dioscorea villosa* cream in the treatment of menopausal syndrome in terms of the objective data.

1.2.3 Third objective

The third objective is to compare the efficacy of *Dioscorea villosa* cream with that of *ProgestoNat* ® cream (McTeer, 2003) in terms of the subjective data gathered in these two studies.

CHAPTER 2

REVIEW OF THE RELATED LITERATURE

2.1 FEMALE REPRODUCTIVE ANATOMY AND PHYSIOLOGY

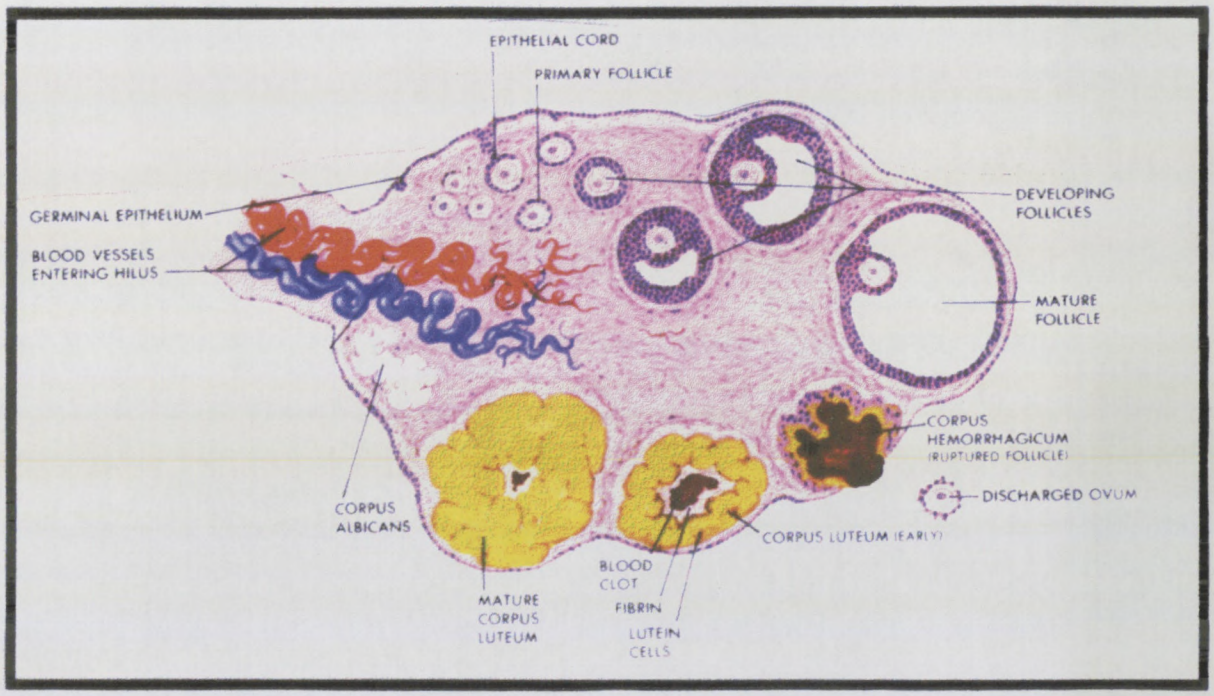
2.1.1 The female reproductive organs

The principal organs of the female reproductive system include the ovaries, fallopian tubes, uterus and vagina (Guyton & Hall, 1997).

The ovary is the main female reproductive organ, which produces ova (egg cells) and steroid hormones in a regular cycle. There are two ovaries, situated in the lower abdomen, one on each side of the uterus. Each ovary contains numerous follicles (Martin, 2000). An infant girl is born with an estimated 500 000 follicles per ovary. Each follicle consists of a single egg that is surrounded by granulosa cells (Cutler & Genovese-Stone, 2000). During childhood the follicles are referred to as primordial follicles, as they consist of only a single layer of granulosa cells. At puberty, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) begin to be secreted in large quantities, resulting in the growth of the ovaries and many of the follicles within them. Each follicle passes through a number of stages of growth before developing into a mature graafian follicle. A graafian follicle consists of a mature ovum, surrounded by layers of granulosa and theca cells. The combination of granulosa and theca cells secrete the ovarian hormones (Guyton & Hall, 1997).

Diagram 2.1

The Structure of the ovary



(Netter, 1977)

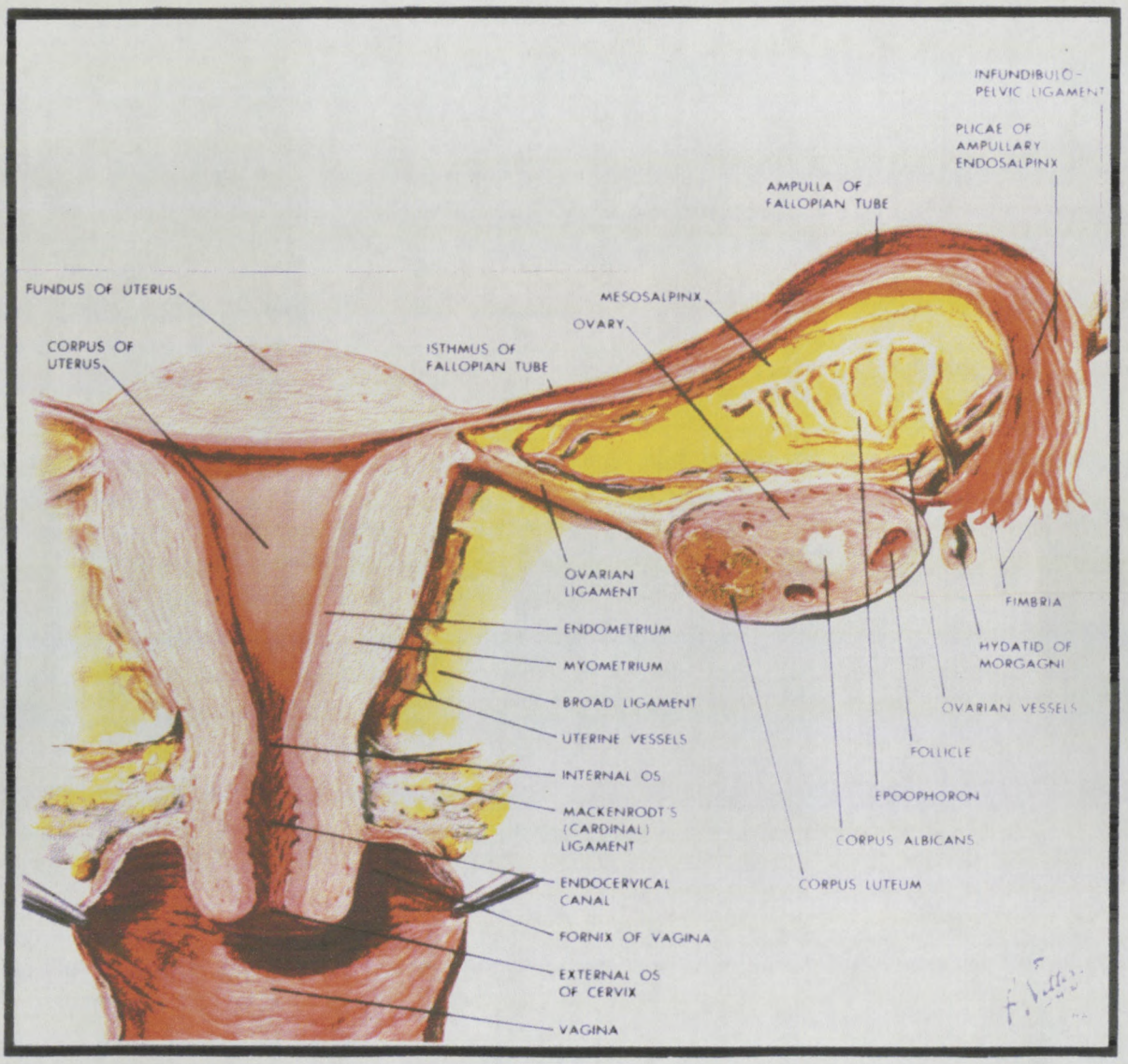
The fallopian tubes are a pair of tubes that conduct the ova from the ovary to the uterus. The ovarian end opens into the abdominal cavity via a funnel-shaped structure with finger-like projections (fimbriae) surrounding the opening. Movements of the fimbriae at ovulation assist in directing the ovum to the fallopian tube (Martin, 2000).

The uterus is the part of the female reproductive system that is specialised for implantation of an embryo in its inner wall and for the growth and nourishment of a fetus. The nonpregnant uterus is a pear-shaped organ suspended in the pelvic cavity by means of peritoneal ligaments. Its upper part is connected to the two fallopian tubes and the lower part joins the vagina at the cervix. The inner lining of the uterus is the endometrium. It is surrounded by a thick wall of smooth muscle, known as the myometrium (Martin, 2000). During menstruation it is the superficial layers of the endometrium, together with blood and leucocytes that are shed and discharged (McKay Hart & Norman, 2000).

The vagina is a muscular tube, lined with a mucous membrane, connecting the cervix of the uterus to the exterior. The wall of the vagina is sufficiently elastic to allow the passage of the newborn child (Martin, 2000).

Diagram 2.2

The Female Reproductive Organs



(Netter, 1977)

2.1.2 The female hormonal system

The female hormonal system consists of the anterior pituitary hormones and the ovarian hormones. The anterior pituitary hormones are follicle-stimulating hormone (FSH) and luteinizing hormone (LH), and the ovarian hormones are estrogen and progesterone. The function of FSH is to stimulate the follicles within the ovaries to grow and LH is necessary for final follicular growth. Estrogen and progesterone are secreted by the ovaries in response to FSH and LH. The function of estrogen is to promote the proliferation and growth of specific sex-related cells in the body and to develop the secondary sexual characteristics of the female. The most important of the estrogens is *estradiol*. Progesterone is concerned with preparation of the uterus for pregnancy and the breasts for lactation (Guyton & Hall, 1997).

2.1.3 The female sexual cycle

The reproductive years of a woman are characterised by monthly rhythmical changes in the rates of secretion of the female hormones and corresponding changes in the sexual organs themselves. This rhythmical pattern is called the female sexual cycle. The duration of the cycle averages 28 days (Guyton & Hall, 1997). The cycle length is measured from the onset of menstrual bleeding (day 1), until the first day of the following menstrual bleed (Cutler & Genovese-Stone, 2000).

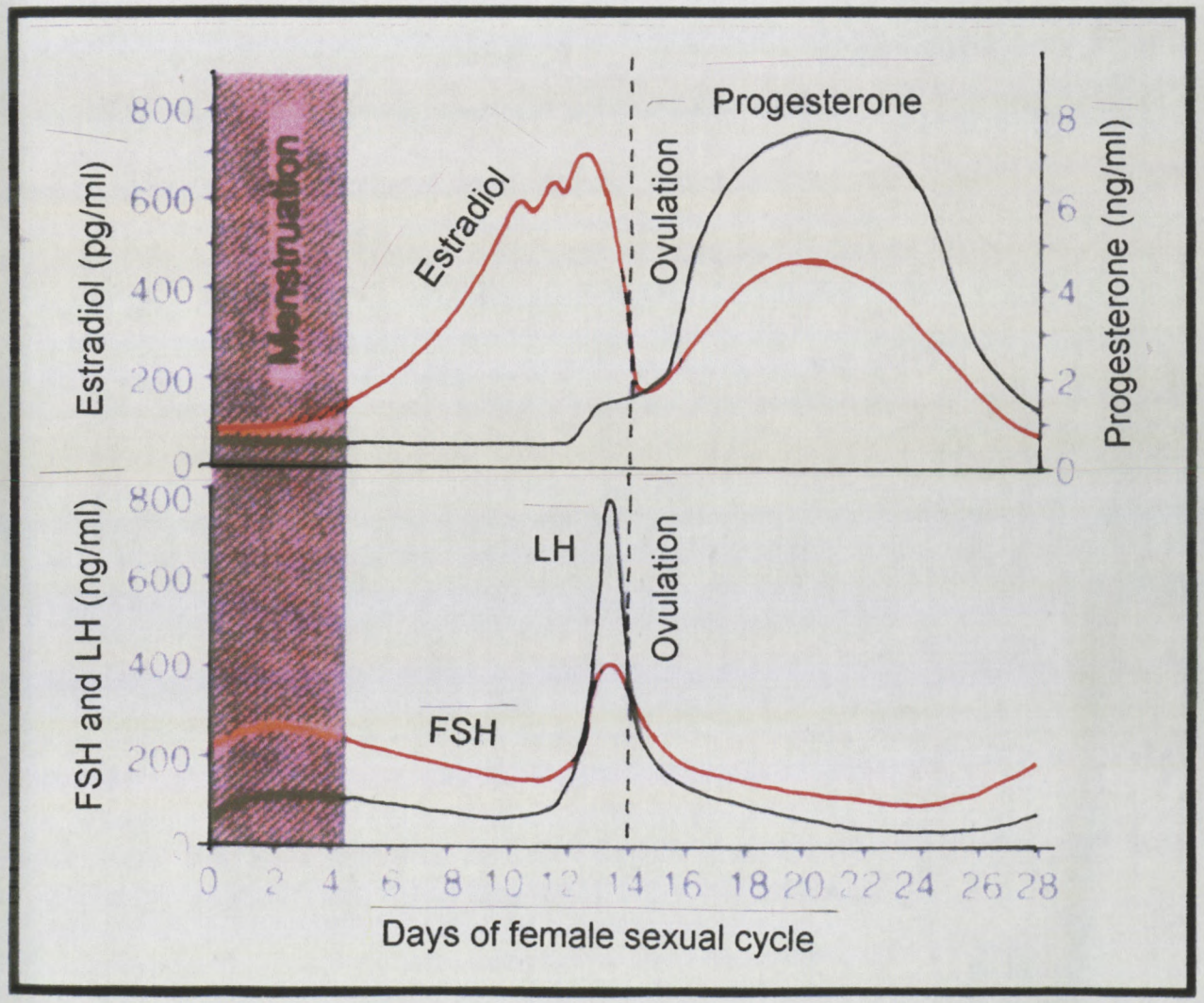
At the beginning of the female sexual cycle, immediately after menstruation, the concentrations of FSH and LH increase and stimulate the follicles in the ovaries to grow. The growth of the granulosa and theca cells is accelerated, and as they grow they secrete a follicular fluid that contains a high concentration of estrogen. After a week or more of growth, one of the follicles begins to outgrow the others, becomes highly developed, and secretes large amounts of estrogen. The remainder of the follicles begin to involute. The high concentrations of estrogen secreted by the dominant follicle cause it to develop rapidly. The estrogen also has a negative feedback effect on the hypothalamus, preventing further secretion of FSH by the pituitary gland. This blocks further growth of the less well developed follicles (Guyton & Hall, 1997).

On approximately the fourteenth day of the cycle, the dominant follicle releases its ovum as a result of surging levels of LH. Following ovulation, the granulosa cells of the ruptured follicle undergo rapid physical and chemical changes, and the follicle becomes what is termed the corpus luteum. The corpus luteum secretes large quantities of both estrogen and progesterone, which thickens the lining of the uterus in preparation for pregnancy. If the ovum is not fertilised, approximately twelve days after ovulation, the corpus luteum loses its secretory function and begins to involute. The levels of estrogen and progesterone begin to decline, reversing the feedback effect on the hypothalamus. The pituitary gland once again begins to secrete FSH and LH. The paucity of estrogen and progesterone secretion leads to menstruation (Guyton & Hall, 1997).

If fertilisation occurs, the developing ovum causes the secretion of the hormone *human chorionic gonadotropin*. Human chorionic gonadotropin prevents involution of the corpus luteum. Instead, it causes the corpus luteum to secrete even larger quantities of estrogens and progesterone. These excess hormones cause the endometrium to continue growing and to store additional nutrients, rather than to be passed in the menstruum (Guyton & Hall, 1997).

Diagram 2.3

Approximate plasma concentrations of the gonadotrophins and ovarian hormones during the normal female sexual cycle



(Guyton & Hall, 1997)

2.2 DEFINITION OF MENOPAUSE AND PERIMENOPAUSE

Menopause is the time in a woman's life when the ovaries cease to produce an ovum every four weeks, menstruation ceases and the woman is no longer able to bear children (Martin, 2000). Menopause is the last stage of a gradual biological process in which the ovaries reduce their production of female sex hormones. This transitional phase begins about three to five years before the final menstruation and is referred to as the climacteric, or perimenopause. Menopause is considered complete when a woman has been without menses for one year (Voda, 1997). The World Health Organisation has defined perimenopause to include the period immediately prior to the menopause (when the endocrinological, biological and clinical features of approaching menopause commence) and the first year after the last menstrual period (Cutler & Genovese-Stone, 2000).

2.3 INCIDENCE

Menopause occurs naturally between the ages of 45 and 55 (McKay Hart & Norman, 2000). The term premature menopause is used if menopause occurs before the age of 40 (Cutler & Genovese-Stone, 2000). Risk factors for premature menopause include familial risk, previous surgery, radiotherapy / chemotherapy, anorexia, over-exercise syndrome, heavy smoking and chronic or acute stress (Jamieson, 2002). Menopause as a result of the surgical removal of both ovaries is referred to as artificial or surgical menopause (Northrup, 1995).

2.4 PHYSIOLOGY OF PERIMENOPAUSE AND MENOPAUSE

Although many older teachings asserted the general concept of low estrogen in perimenopause, this idea is not supported by most recent studies. A study comparing hormonal levels of women in their perimenopausal years with those in their midreproductive years concluded that the women in their perimenopausal years circulated higher levels of estrogen throughout the cycle than the younger women. The increase in FSH levels at the beginning of perimenopause results in stimulation of a large number of follicles in the ovaries. The greater number of swelling follicles causes a large production of estrogen. Examination of the ovaries of early perimenopausal women will often show a greater number of follicles swelling and producing estrogen. This process appears to continue until the follicular supply has been exhausted (Cutler & Genovese-Stone, 2000).

In the early stage of perimenopause, the corpus luteum continues to secrete progesterone, but in diminishing amounts. The net balance between estrogen and progesterone is greatly in favour of estrogen. The changes in the levels of estrogen are more variable. This results in a state of estrogen dominance during early perimenopause. The inability of the aging ovary to produce progesterone characterises and defines the perimenopausal transition (Cutler & Genovese-Stone, 2000).

In the end stages of perimenopause, the ovaries continue to shrink and become less receptive to the effects of FSH and LH, either because the number of

receptor binding sites on the follicles decrease, or because increasing numbers of follicles are decreasing, or both. The effect is that estrogen secretion declines and fluctuates and anovulation becomes more frequent. The fluctuations are a major factor in causing the symptoms associated with perimenopause. As the years pass, fewer follicles are left in the ovaries, and the level of estrogen begins to fall more rapidly. With a decrease in the levels of estrogen, there is no longer a negative-feedback effect on the hypothalamus, resulting in rising levels of FSH and LH. Eventually, the cycles cease altogether, signifying menopause (Llewellyn-Jones, 1999).

2.5 SYMPTOMS OF PERIMENOPAUSE

During perimenopause, the hormone levels do not decline uniformly. The main reason for the symptoms experienced during perimenopause is hormonal imbalance (Glenville, 1997). Some of the symptoms that occur include vasomotor symptoms such as hot flushes, night sweats, palpitations and headaches; psychological symptoms such as depression, irritability, memory loss and anxiety, and urogenital symptoms such as urinary incontinence, vaginal dryness and loss of libido (Morris & Rymer, 2001). Other symptoms that may occur include fatigue and lethargy, muscle and joint pains, water retention, breast tenderness, bloating and menorrhagia or oligomenorrhoea (Jamieson, 2002).

2.5.1 Hot flushes and night sweats

A hot flush is a sudden sensation of intense heat that usually begins on the face, neck, head or chest and then spreads to the rest of the body and may become generalised (Llewellyn-Jones, 1999). Each hot flush may last from a few minutes to 30 minutes and is often accompanied by sweating and palpitations. If hot flushes occur at night, they are referred to as night sweats (Mattox, 1998). Seventy-five percent of menopausal women experience hot flushes. Eighty percent of those who experience hot flushes endure them for longer than 1 year and fifty percent for longer than 5 years (Hoover & Wallach, 2002).

The flushing is associated with peripheral vasodilatation and a temporary rise in body temperature of 3°C (Llewellyn-Jones, 1999). However, the core temperature, as recorded in the oesophagus, rectum, vagina and tympanic membrane, falls due to the heat losing effect of peripheral vasodilatation. The exact mechanism of the hot flush remains unknown, however it is generally considered that it is, in part, due to a disturbance of the thermoregulating centre (Sturdee, 1997). Hot flushes correspond closely with a surge in LH levels before the event, and tend to become more frequent as ovarian function diminishes (Dell & Stewart, 2000).

2.5.2 Psychological symptoms

Recognised psychological symptoms include mood swings, anxiety, depressed mood, insomnia, irritability, forgetfulness, poor concentration and fatigue (Morris & Rymer, 2001). Women who are depressed during the menopausal transition are more commonly those who have had a surgical menopause, and those who hold negative beliefs about the menopause (Sturdee, 1997). At a neuroregulatory level in the brain, estrogen functions as both a serotonin agonist and a cholinergic agonist. It has mixed effects on endorphins, decreases dopamine receptors and increases γ-aminobutyric acid (GABA) activity, which suggests that estrogen may have a role in mediating mood. However, reports in the literature are inconsistent about whether there is an association between menopause and depressed mood. As women become postmenopausal, the rates of depression tend to decline, independent of any previous history of depression (Dell & Stewart, 2000).

2.5.3 Stress incontinence

Stress incontinence refers to the involuntary loss of urine under conditions which increase the intra-abdominal pressure, such as coughing or physical exertion (Nel, 1996). The exact mechanism of the development of stress incontinence in some menopausal women is not entirely understood. However, it is thought that estrogen is necessary to maintain the elasticity and strength of the urinary tract as estrogen receptors are present in the tissues of the bladder, urethra and muscles of the pelvic floor (Morris & Rymer, 2001).

2.5.4 Vaginal dryness

The lining of the vagina consists of many layers of cells that are estrogen – sensitive. When estrogen levels fall, the lining of the vagina becomes thinner and loses elasticity and lubrication. This is called vaginal atrophy (Northrup, 1995). Vaginal atrophy results in symptoms of vaginal dryness, such as irritation, burning, pruritis, discharge, painful intercourse, bleeding and a decrease in vaginal secretions (Gambrell, 1997). Vaginal atrophy may also be accompanied by an increase in the pH of the vagina, resulting in bacterial vaginitis (Northrup, 1995).

2.5.5 Loss of libido

Loss of sexual interest during perimenopause may be as result of psychological, hormonal or physical influences. Loss of vaginal moisture makes intercourse uncomfortable, and even painful (Morris & Rymer, 2001). A decrease in pheromonal secretion that occurs during menopause makes women feel less attractive and appealing. With falling estrogen levels, a woman's receptive sex drive disappears, and if testosterone levels fall her aggressive sex drive disappears too. However, a woman's attitude towards menopause has a substantial influence on her libido (Wassermann, 1999).

2.6 LONG-TERM EFFECTS OF MENOPAUSE

The symptoms that occur during perimenopause are as a result of fluctuating estrogen levels. However, once menopause is established, the estrogen levels fall dramatically, and remain low. Estrogen deficiency increases the risk of osteoporosis, cardiovascular disease and alzheimer's disease (Llewellyn-Jones, 1999).

2.6.1 Osteoporosis

Osteoporosis is a disease characterised by low bone mass and microarchitectural deterioration of bone tissue leading to enhanced bone fragility and a consequent increase in fracture risk. Peak bone mass (PBM), the maximum amount of bone attained throughout life, is achieved toward the end of the second decade. From attainment of PBM, very little bone is lost until perimenopause. Bone loss is most rapid in early perimenopause and occurs mainly in trabecular bone (spine) and later in cortical bone (hips) (Ballard & Purdie, 1997).

Hormonal influences on bone integrity were previously focussed on estrogen's role in preventing bone resorption. However, accumulating evidence confirms that progesterone has a role in bone formation that is synergistic with that of estrogen. The annual loss of up to 3% of bone mass during perimenopausal transition is largely due to the imbalance of estrogen to progesterone. It is

hypothesised that the following 3 changes that occur during perimenopause account for the rapid loss of bone:

1. Wide swings in estrogen provoke increased bone resorption.
2. The stress of variable menstrual cycles and increased cortisol causes increased bone resorption and low bone formation.
3. Less circulating progesterone leads to less bone formation.

The imbalance of estrogen to progesterone is less drastic by the time of menopause. Consequently, the bone loss declines to 1% per annum (Cutler & Genovese-Stone, 2000).

2.6.2 Cardiovascular disease

The incidence of Cardiovascular disease (CVD) in young women is low, but increases significantly in the sixth decade of life, which correlates with the onset of natural menopause. This had led to the hypothesis that menopause-induced hormonal changes are independently associated with acceleration of the atherosclerotic process (Reis, Zell & Holubkov, 1997). The cardiovascular properties of estrogens have been investigated for decades, but are not yet fully understood in detail (Finking et al. 2001).

Menopause may increase the risk of CVD indirectly, by unfavorably altering the lipid profile, or directly by altering vascular properties (Reis, Zell & Holubkov, 1997). Estrogen deficiency results in an increase in total and low density

lipoproteins (LDL) and a reduction in high density lipoproteins (HDL) (Whitehead, 1998). High levels of LDL cholesterol correlate directly with the risk of CVD, as LDL is incorporated into atheromatous plaques on the blood vessel walls. HDL however, protects against CVD as it removes cholesterol from the blood vessels and transports it back to the liver (Edwards, 1995). In vitro studies demonstrate that estrogen inhibits arterial endothelial cell hyperplasia and intimal thickening, and human studies show that estrogen prevents abnormal coronary artery constriction. Therefore it has been postulated that the loss of estrogen during menopause is associated with acceleration of arterial lipid deposition, endothelial cell hyperplasia and intimal thickening, which are early manifestations of atherosclerosis (Reis, Zell & Holubkov, 1997).

2.6.3 Alzheimer's disease

Alzheimer's disease (AD) is a progressive degenerative disease of the brain, which leads to destruction of the cortical nerve cells, finally resulting in atrophy of regions of the brain (Panidis et al. 2001). The incidence of Alzheimer's disease increases more in women than in men after age 65, with age-specific rates varying from 1.5 to 3.0 times that of men (Gambrell, 1997). Alzheimer's disease is subdivided into early-onset (below 65 years) and late-onset disease. Early-onset Alzheimer's disease is largely due to genetic mutations, whereas late-onset disease is influenced by exogenous factors. For women, one such factor may relate to postmenopausal estrogen deprivation (Henderson, 1998).

Estrogen is known to exert many metabolic and structural changes in the central nervous system (CNS), including promotion of growth of cholinergic neurones (Sturdee, 1997). Other estrogen effects include the increase of cerebral blood flow and the augmentation of cerebral uptake and utilisation of glucose, thereby enhancing brain function (Henderson, 1998). Therefore, estrogen deficiency is thought to contribute to the neurodegenerative changes of the CNS and increase the incidence of senile dementia (Gambrell, 1997).

2.7 MANAGEMENT OF MENOPAUSE

2.7.1 Hormone Replacement therapy

Hormone replacement therapy (HRT) is the use of female hormones (estrogens, progestogens and androgens) for the relief of symptoms resulting from cessation of ovarian function, either at the time of natural menopause or following surgical removal of the ovaries (Martin, 2000). The use of progestogens together with estrogens in HRT is referred to as opposed therapy. The different routes of hormone administration include oral, transdermal, subcutaneous, vaginal and intra-uterine (Jamieson, 2002).

Each individual should assess the risk / benefit ratio in order to evaluate the appropriateness of long-term therapy with HRT. This involves carefully considered medical judgement, as the benefits and risks are not directly comparable (Dreyer, 1999).

2.7.1.1 Benefits of HRT

HRT can reduce or eliminate the short-term symptoms of perimenopause, i.e.:

- Relieves vasomotor symptoms – Hot flushes and night sweats
- Prevents vaginal atrophy – Relieves vaginal dryness and painful intercourse
- Relieves depressed mood

In order to obtain long term benefits from HRT, such as reduced risk of osteoporosis and cardiovascular disease, therapy must be sustained for at least seven years (Dreyer, 1999). HRT may also prevent the development of Alzheimer's disease, but is not appropriate for its treatment (Panidis et al. 2001).

Osteoporosis

Hormone Replacement Therapy is often prescribed for the prevention and treatment of osteoporosis. However, when estrogens are discontinued, bone loss begins again. Therefore, long-term (even life-long) therapy is needed to prevent fractures. Since hormonal imbalance is not the sole risk factor for osteoporosis, a complete evaluation of each patient is required before commencement of treatment (Lindsay, 1998). Other risk factors for osteoporosis include white race, female sex, low body mass index, smoking and a positive family history of osteoporosis (Panidis et al. 2001). The following measures may be taken to prevent osteoporosis; daily calcium intake of 1-1.5g, regular weight bearing exercise, avoidance of smoking and reduced salt intake (Llewellyn-Jones, 1999).

Cardiovascular disease

Observational studies have found lower rates of coronary heart disease in postmenopausal women who take estrogen than in women who do not. This association has been reported to be especially strong for secondary prevention in women with coronary heart disease. However, this potential benefit has not

been confirmed in clinical trials. The heart and Estrogen / Progestin Replacement Study (HERS) was the first randomised, placebo controlled trial to determine if estrogen plus progestin therapy alters the risk for coronary heart disease events in postmenopausal women with established coronary disease. During an average follow up of 4.1 years, the treatment group showed no reduction in the overall risk for coronary heart disease events. However, the therapy did increase the risk of venous thromboembolic events and gallbladder disease. The American Heart Association concluded that there was insufficient data to support initiation of HRT for the sole purpose of secondary prevention of coronary heart disease. However, the pattern of coronary heart disease events after several years of therapy is more favourable. Therefore women already receiving therapy are advised to continue (Hulley et al. 1998).

The risk of coronary heart disease may be significantly reduced through moderate intensity physical activity. The recommended activity is 30 minutes per day on most days of the week. These levels of activity are associated with a reduced risk of coronary heart disease even among women who are overweight, smoke or have elevated cholesterol levels (Lee et al. 2001).

2.7.1.2 Risks of HRT

Long-term administration of HRT is associated with an increased risk of endometrial cancer, ovarian cancer, breast cancer, thromboembolic disease and hypertension (Dreyer, 1999).

Endometrial cancer

There is a 2 to 3 fold greater risk of endometrial cancer in women taking unopposed HRT. However, this risk is eliminated by the addition of at least 12 days of progestin therapy each month (Hoover & Wallach, 2002).

Estrogen stimulates the growth of the endometrial lining of the uterus, which results in endometrial hyperplasia and ultimately endometrial cancer. Therefore, progestogens are administered together with estrogens (opposed HRT) to prevent endometrial stimulation. It is suggested that all women that still have a uterus should receive opposed therapy (Dreyer, 1999). However, progestogens can cause some undesirable symptoms, such as depression, irritability, mastalgia, abdominal distention, migraine-like headaches and endometrial withdrawal bleeding (Patriarca et al. 2001).

Ovarian cancer

Epidemiologic studies of the association between postmenopausal estrogen use and ovarian cancer have had inconsistent results. A large prospective study recently examined the association between postmenopausal estrogen use and ovarian cancer mortality. The conclusion was that postmenopausal estrogen used for 10 or more years was associated with increased risk of ovarian cancer mortality that persisted up to 29 years after cessation of use (Rodriguez et al. 2001).

Breast cancer

The issue of the association between breast cancer and HRT is a very controversial one. Some studies have revealed an increase risk of breast cancer in women taking HRT, but others have not (Hoover & Wallach 2002). A recent study, the Women's Health Initiative (WHI) randomised controlled trial, assessed the risks and benefits of estrogen plus progestin in healthy postmenopausal women. The trial was stopped early based on health risks that exceeded health benefits over an average follow up of 5.2 years. Women in the treatment group experienced an increase in cardiovascular events by 29%, a 2-fold increase in venous thromboembolism, deep vein thrombosis and pulmonary embolism, and 26% increase in breast cancer relative to the placebo group. Endometrial cancer and lung cancer incidences were not affected. There was a significant decrease in hip and vertebral fractures. The WHI is the first randomised controlled trial to confirm that combined estrogen and progestin increases the risk of breast cancer significantly and does not confer benefit for preventing cardiovascular disease (Rossouw et al. 2002).

2.7.1.3 Side-effects of HRT

Common side-effects related to HRT include mastalgia, water retention, weight gain, headache, premenstrual syndrome, mood changes dysmenorrhoea and irregular bleeding (Jamieson, 2002).

2.7.1.4 Contraindications to HRT

If a woman has a history of any of the following disorders, she should be cautioned against the use of HRT:

- Distant or recent history of breast cancer
- Undiagnosed abnormal vaginal bleeding
- Acute vascular thrombosis or emboli
- Liver dysfunction or disease
- Known or suspected estrogen-dependent neoplasms
- Pregnancy

(Hoover & Wallach, 2002)

2.8 ALTERNATIVE MANAGEMENT OF THE MENOPAUSE

Menopausal women account for one of the largest segments of alternative medicine users, with 80% of women aged 45 – 60 using alternative therapies for the management of menopausal symptoms. These therapies include homoeopathy, herbal remedies, meditation, traditional chinese medicine, vitamins and minerals, acupuncture and chiropractic practices (Kang, Ansbacher & Hammoud, 2002). The reasons for their interest in these therapies include:

1. Dissatisfaction with conventional medicine as ineffective, impersonal, costly, or yielding adverse outcomes.
2. A need for personal control, viewing alternatives as authoritarian and affording greater personal autonomy.
3. A perception that alternatives are more compatible with personal values and ethical and religious beliefs (Taylor, 2001).

2.8.1 Homoeopathy

Homoeopathy is a self-consistent scientific system of medicinal therapy, developed in 1796 by Christian Friedrich Samuel Hahnemann (1755 – 1843) (Gaier, 1991). It is based on the principle of 'like cures like'. This means that a medicine capable of producing certain effects when taken by a healthy human being is capable of curing any illness that displays similar effects. Medicines are administered in small doses, prepared by the process of potentisation; a step by

step dilution and shaking-like action of the drug that makes it extremely powerful and simultaneously renders it harmless (Sankaran, 1997).

Homoeopathy treats the patient as a whole and as an individual. There is no specific medicine for any particular disease, but there is a medicine for the patient suffering from the disease. The homoeopath takes into consideration all the symptoms that distinguish a person as an individual, including mental, general and physical symptoms. A remedy is then prescribed for the patient that best represents the individual. This remedy is the *similimum* (Sankaran, 1997).

Hagen (1995) conducted a study to determine the effectiveness of the homoeopathic similimum on menopausal syndrome in terms of the patients' perception of the treatment. In conclusion of the study, the treatment group showed a 33% greater improvement than the placebo group in terms of the Psychological General Well-Being Index, and a 40% greater improvement over the placebo group in terms of the patient perception of treatment and hot flush questionnaire.

Richardson (2001) conducted a patient benefit survey for the Liverpool Regional Department of Homoeopathic Medicine. Patients attending the clinic over a 12 month period were assessed using the Glasgow Homoeopathic Hospital Outcome Score (GHHOS), a questionnaire in which the patient is asked to grade his / her own response to homoeopathic treatment. The scores range from –4

(disastrous deterioration) to +4 (cured / back to normal), with 0 representing no change. 3.3% of the patients attending the clinic were treated for menopausal symptoms. 86.1% of these patients reported improvement, with 69.4% reporting moderate improvement, significant improvement or complete improvement. A similar study was conducted by Clover (2000) for the Tunbridge Wells Homoeopathic Hospital. Patients were assessed over a 12 month period according a scoring method similar to that mentioned above (GHHOS). Patients being treated for menopausal symptoms accounted for 3.8% of the total number of patients attending the clinic. 79% of these patients reported improvement in menopausal symptoms. These studies give an indication of the benefit homoeopathic treatment may have on menopausal symptoms.

2.8.2 Nutritional therapy

Several nutrients may be used to help relieve some of the symptoms of perimenopause:

- Vitamin E has been shown to relieve vaginal dryness by increasing the blood supply to the vaginal wall, and to help relieve hot flushes (Pizzorno & Murray, 1999). It also aids in preventing heart disease by keeping LDL cholesterol from adhering to artery walls (Wilmont, 1999).
- Vitamin C and flavonoids may reduce the heavy menstrual bleeding that often occurs during perimenopause by strengthening the capillary walls that weaken just before and during menstruation (Wilmont, 1999). Vitamin C in

combination with hesperidin may be effective in relieving hot flushes (Pizzorno & Murray, 1999).

- Gamma-oryzanol (ferulic acid) is a growth-promoting substance found in grains and isolated from rice bran oil. It relieves hot flushes by enhancing pituitary function and promoting endorphin release by the hypothalamus. It has also been shown to be effective in lowering blood cholesterol triglyceride levels (Pizzorno & Murray, 1999).
- Calcium should also be supplemented, in combination with vitamin D, to prevent osteoporosis (Pizzorno & Murray, 1999).

2.8.3 Phytotherapy

Phytotherapy is an empirical system of medicine that employs only plant remedies derived from trees, ferns, seaweed, lichens or other vegetation (Gaier, 1991). The effect of these remedies is thought to be as a result of phytoestrogens, weak estrogens of plant origin. They are presumed to competitively bind to estrogen receptors (Dell & Stewart, 2000).

- *Cimicifuga racemosa*, commonly known as black cohosh, is an indigenous eastern North American plant that has been used by Native Americans for gynaecological conditions for many years. It was called ' squaw root' because it was used primarily for female disorders (Kang, Ansbacher & Hammoud, 2002). Black cohosh is reported to relieve hot flushes, depression, anxiety and vaginal atrophy. The exact mechanism of action is not know,

however black cohosh has been shown to suppress LH secretion, which surges just before a hot flush is experienced. Black cohosh does not increase estrogen levels in the blood. Instead, it appears to bind to estrogen receptors in order to mimic the effects of the weak estrogen *estriol* (Faloon, 2002).

- *Vitex agnus-castus* (Chaste berry) improves hot flushes, depression and vaginal dryness (Wilmont, 1999). It reduces prolactin levels and increases the production of progesterone, helping to correct hormonal imbalances (Briffa, 2002). Chaste berry is also used to enhance libido in postmenopausal women, and improves irritability, mood changes, anger headache and breast fullness in premenstrual syndrome (Taylor, 2001).
- *Angelica sinensis* (Dong quai) is a native herb to eastern Asia and China. It has been used for more than 1000 years in traditional chinese medicine for the treatment of dysmenorrhoea, irregular menstruation and as a supportive herb for menopausal complaints (Kang, Ansbacher & Hammoud, 2002).
- *Glycyrrhiza glabra* (liquorice) is believed to lower estrogen while simultaneously raising progesterone levels (Pizzorno & Murray, 1999). The chinese have successfully used liquorice extracts for more than 3000 years to treat menopausal symptoms (Faloon, 2002).
- *Ginkgo biloba* is often indicated in menopausal women for its effects on the vascular system. It helps with forgetfulness by increasing blood flow to the brain and improving the transmission of nerve signals in the brain (Pizzorno & Murray, 1999).

- *Panax ginseng* is promoted for a wide array of complaints and disorders. It is reported to have estrogenic properties and to boost immunity, energy and vigor (Kang, Ansbacher & Hammoud, 2002).

Phytoestrogens

Phytoestrogens are plant-based, naturally occurring estrogens with a chemical structure and function similar to endogenous estrogens. The 4 main classes of phytoestrogens are isoflavones, lignans, coumestans and resorcylic acid lactones. Isoflavones are found in soy products, and lignans are found mainly in flaxseed. Phytoestrogens have been shown to bind to estrogen receptors, demonstrating both agonist and antagonist effects (Balk, 2001).

Clinically, phytoestrogens appear to protect against cardiovascular disease. Soy protein is thought to decrease total cholesterol and LDL cholesterol and possibly increase HDL cholesterol. The risk of osteoporosis appears to be decreased by the consumption of soy, however the dosage of soy necessary to maintain bone density is unknown. Clinical trials have attempted to address whether soy will reduce the incidence of menopausal symptomatology, but the results are inconsistent. More work remains to be done to fully understand the risks, benefits and side-effects of phytoestrogen consumption (Balk, 2001).

2.9 *DIOSCOREA VILLOSA*

Commonly known as Wild Yam, *Dioscorea villosa* is a native plant of North and Central America. The root was first used medicinally by the Aztecs and Maya for its pain-relieving qualities. It is now hailed as a natural alternative to HRT, even though it has not as yet been proved for this purpose (Wilmont, 1999).

Wild Yam is used in a cream form to relieve the symptoms of menopause or premenstrual syndrome. When taken in capsule, tincture or tea form, wild yam acts as a muscle relaxant, targeting muscles in the abdomen and pelvis. This benefit is due to the alkaloids contained in the herb. It also contains steroidal saponins that help alleviate muscle strains, muscle pain and arthritis (Wilmont, 1999).

Wild yam is often confused with Natural progesterone. *Diosgenin*, extracted from wild yam is converted *in vitro* to 'Natural Progesterone', so called because it has the identical chemical structure to the progesterone made in the body. However, it is not known whether the body is able to make this conversion itself. The effect of wild yam in its pure state is very different from that of the synthesised 'natural' progesterone discussed above. As is the case with many effective herbs, it is not known precisely how wild yam acts on the body. The essence of herbal medicine is that all the ingredients in a herb work together to help towards the overall therapeutic effect. Herbs contain a variety of substances; active substances, balancing substances and substances that cope with any side

effects of the active substances. Therefore herbs are more effective when used in their naturally occurring form (Glenville, 1997).

In contrast to natural progesterone, Progestins / Progestogens are synthetically produced steroid hormones that are prescribed in hormone replacement therapy. The effect of progestogens alone in the context of menopause is not known as investigations involve the administration of estrogen alongside progestogens to prevent endometrial stimulation. However, progestogens are commonly blamed for causing depression, weight gain, bloating and adversely affecting serum lipids (Morris & Rymer, 2001). Other observed side effects include breast tenderness, irritability and abnormal uterine bleeding (Whitehead, 1999).

A recent study researched the effects of wild yam extract on menopausal symptoms, lipids and sex hormones in healthy postmenopausal women whose average time since last menstrual period was 4.3 to approximately 0.9 years. The double-blind, placebo-controlled, cross-over study included 23 healthy postmenopausal women suffering from symptoms of menopause. Each participant was given active cream and matching placebo for 3 months in random order. The active cream contained *Dioscorea villosa* extract, *Linum Usitatissmum* oil, *Perlargonium graveolens* oil, *Salvia officinalis* oil and α-tocopheryl acetate in a vegetable-based cream. In conclusion, the study revealed that while short-term use with topical wild yam extract is free of adverse

effects, it has little effect on menopausal symptoms, hormones, lipids or blood pressure (Komesaroff et al. 2001).

Another study researched the effect of transdermal progesterone cream for vasomotor symptoms and postmenopausal bone loss. *Diosgenin* was extracted from wild yam and converted into natural progesterone. The progesterone cream contained 20mg of natural progesterone per quarter teaspoon. After 1 year of treatment, although there was no improvement in bone density, there was a significant improvement in hot flushes of 83% in the treatment group (Leonetti, Longo & Anasti, 1999).

2.10 SUMMARY

Hormone replacement therapy is the most frequently employed treatment for the management of menopausal symptoms. Many women are now seeking alternatives to hormonal therapies as they are costly and have many side-effects. Among the alternative therapies available is *Dioscorea villosa*. However there have been no studies as to its safety or efficacy in the management of perimenopausal symptoms.

CHAPTER 3

MATERIALS AND METHODS

3.1 STUDY DESIGN

Thirty female subjects were selected to participate in the study. They were randomly divided into two equal groups of 15 subjects per group. Group 1 was the Treatment group receiving *Dioscorea villosa* cream, and group 2 was the Placebo group. The placebo cream given to group 2 was indistinguishable from the experimental cream. It contained the identical combination of ingredients with exception to that of *Dioscorea villosa* (see Appendix C). The researcher explained to the participants that there was a 50% chance of being placed in the placebo group. As compensation, the subjects in the placebo group were offered free treatment for menopausal syndrome after the study.

The data gained from the patients in the placebo group (group 2) were shared with a concurrent study of similar methodology (The efficacy of *ProgestoNat* ® cream in the treatment of menopausal syndrome, McTeer, 2003) and vice versa. This was possible, as the placebo applications used in the two studies were identical in terms of ingredients, appearance, dosage and posology. The subjective and objective measurements in the two studies were also identical.

3.2 RECRUITEMENT PROCEDURE

Advertisements were placed in local newspapers, advertising the study and asking for volunteers between the ages of 40 – 55 years, currently experiencing menopausal symptoms. An article was placed in a major regional newspaper that explained the use of and the difference between *Dioscorea villosa* and Natural progesterone creams. The article called for volunteers to participate in the study.

3.3 SELECTION CRITERIA

Subjects who volunteered to participate in the study were assessed according to the following criteria:

3.3.1 Inclusion criteria

Subjects had to be between 40-55 years of age and experiencing at least 2 major and 1 minor of the following symptoms:

MAJOR SYMPTOMS:

- Hot flushes
- Menstrual irregularities
- Dry vaginal canal / painful intercourse
- Irritability and mood changes

MINOR SYMPTOMS:

- Headaches
- Stress incontinence
- Memory loss
- Loss of libido
- Tinnitus
- Bleeding gums

(Margolis, 2002)

3.3.2 Exclusion criteria

- Subjects who were on hormone replacement therapy (HRT) or any other treatment (including herbal remedies) for menopausal symptoms.
- Subjects experiencing premature menopause or any other condition in which estrogen production is deficient.
- Subjects who had had a total hysterectomy.
- Subjects who were on any other medication such as thyroxin, psychotropic drugs or corticosteroids which may have affected the presentation of menopausal symptoms.

Subjects who met with all the parameters were given a patient information letter (see Appendix A) and were required to sign an informed consent form (see Appendix B) before participating in the study.

3.4 RANDOMISATION

This randomised placebo controlled trial was conducted in a double blind manner. Randomisation was conducted by Dr David Naudé (Department of Homoeopathy, Durban Institute of Technology). Either group 1 or group 2 was randomly allocated to a list of numbers from 1 – 30. A number was allocated to each subject sequentially, thereby placing them in one of the two groups. The creams were packaged individually, with the corresponding subject number written on the packet.

3.5 TREATMENT

Subjects were required to attend three consultations with the researcher. Subjects who were still menstruating regularly were required to attend the consultations between the first and the third day of the menstrual cycle. Subjects who were menstruating irregularly but who had had their last menstrual period within the past 12 months were monitored according to calendar months.

During the first consultation each subject was required to complete the Greene Climacteric Scale questionnaire (see Appendix D). A blood sample was taken by a registered professional nurse. A strict safety protocol was adhered to during the procedure. The progesterone level in the blood was measured at the Nelson Mandela School of Medicine, University of Natal, Department of Chemical Pathology. Data obtained from the questionnaire and blood analysis at the first consultation formed the baseline for statistical analysis. Subjects were given a

container of either *Dioscorea villosa* cream or placebo cream, according to their allocated group. A metered dose (20 mg) (one pump action) of the cream was applied every night, on a rotational basis to the face, neck, upper chest, breasts, inner arms and thighs, palms of hands and soles of feet.

The second consultation took place after one menstrual cycle or within 28 - 35 days if menstruation did not occur. During this consultation the Greene Climacteric Scale questionnaire was completed for the second time. The third consultation was held within the same time period as the second consultation. During this consultation the Greene Climacteric Scale questionnaire was completed for the third and final time. A second blood sample was drawn for the progesterone level to be measured.

The creams were prepared by Natura Homoeopathic Laboratories (a registered homoeopharmaceutical company) according to the standards set out in the British Pharmacopoeia (British Pharmacopoeia, 1999). The experimental treatment consisted of an aqueous cream base comprising seven base substances (i.e. *Aloe vera* (1%), *Borage oil* (3%), *Calendula officinalis* (1%), *Echinacea angustifolia* (1%), *evening primrose oil* (1%), *Piper methysticum* (1%), *Symphytum officinale* (1%) and Vitamin E (1%)). This base substance was then impregnated with the test substance, *Dioscorea villosa* at 2% volume to volume (see Appendix E).

The placebo cream consisted of the aqueous cream base alone (with the seven above-mentioned base substances in identical proportions). Both creams were indistinguishable in terms of packaging, colour and odour, thus ensuring the double-blind methodology.

3.6 MEASUREMENT

3.6.1 Subjective data

During each of the three consultations, subjects completed the Greene Climacteric Scale questionnaire (See appendix D). This questionnaire is a brief but comprehensive and valid measure of climacteric symptomatology. The scale is based on climacteric symptoms that are divided into four groups, namely psychological (anxiety and depression), somatic, vasomotor and sexual. Each symptom is given a score ranging from 0 to 3. A score of 0 represents no symptom experienced and 3 represents extreme symptoms. Each group of symptoms is totalled separately and not added together to give a single score (Greene, 1998). Data obtained at the first consultation served as a baseline measurement for statistical purposes.

3.6.2 Objective data

During the first and third consultations, a blood sample was drawn from each subject by a registered nurse. The samples were appropriately labelled and taken to the Nelson Mandela School of Medicine, University of Natal, Department

of Chemical Pathology. The blood samples were centrifuged at 3000rps for 10 minutes. The serum was poured into a tube and stored at -20°C. This process was performed for each blood sample within two hours of drawing the blood. The progesterone test was performed on all the serum samples simultaneously at the end of the study. This was done in order to minimise error and ensure standardisation. Data obtained at the first consultation served as a baseline measurement for statistical purposes. The method of analysis used was Elecsys Progesterone II, a product of Roche Diagnostics corporation.

3.7 DATA ANALYSIS

3.7.1 Statistical methods

The two variables of interest in this study were the subjective data (i.e. the score of symptoms from the Greene Climacteric Scale questionnaire) and the objective data (i.e. the progesterone measurements) respectively. The score of symptoms from the Greene Climacteric Scale questionnaire is further subdivided into four variables, namely psychological (anxiety + depression), somatic, vasomotor and sexual. Three sets of symptom scores (subjective data) and two progesterone readings (objective data) were taken for each subject.

Due to the relatively small sample size (n = 30), the two variables were analysed using non-parametric tests.

3.7.2 Statistical analysis

All statistical analyses were carried out using SPSS version 9.0.

PROCEDURE 1 – MANN-WHITNEY U TEST

The Mann-Whitney U test was used to determine whether there were significant differences between the two groups with respect to the variables of interest (Inter group comparative purposes).

(i) **Hypothesis testing**

The null hypothesis H_0, states that there is no difference between the groups at the α= 0.05 level of significance. The alternative hypothesis H_1, states that there is a difference between the groups.

(ii) **Decision rule**

At the α=0.05 level of significance, the null hypothesis is rejected if $p < \alpha$ where p is the observed significance level. Otherwise, the null hypothesis is accepted at the same level of significance.

PROCEDURE 2 – FRIEDMAN'S TEST

Friedman's test was used to determine whether there were significant improvements within each of the groups with respect to the subjective data (Intra group comparative purposes).

(i) **Hypothesis testing**

The null hypothesis H_0, states that there is no difference between the visits at the α= 0.05 level of significance. The alternative hypothesis H_1, states that there is a

difference between the visits.

(ii) **Decision rule**

At the α=0.05 level of significance, the null hypothesis is rejected if $p < \alpha$ where p is the observed significance level. Otherwise, the null hypothesis is accepted at the same level of significance.

PROCEDURE 3 – DUNN PROCEDURE

If the null hypothesis H_0 was rejected for Friedman's T test, then the Dunn Procedure was performed in order to identify which of the consultations were different.

Method:

If R_j and $R_{j'}$ are the j^{th} and j'^{th} treatment rank totals, then we declare R_j and $R_{j'}$ significantly different if:

$$|R_j - R_{j'}| \geq z \sqrt{\frac{bk(k+1)}{6}}$$

Where:

z = a value in the standard normal probabilities table corresponding to

$1-[\alpha/k(k-1)]$

α = experimentwise error rate

k = the number treatments (i.e. the total number of consultations)

b = the number of blocks (i.e. the total number of patients in the group)

(Daniel, 1978)

PROCEDURE 4 – WILCOXON SIGNED RANK TEST

Wilcoxon signed rank test was used to determine whether there were significant improvements within each of the groups with respect to the objective data (Intra group comparative purposes).

(i) Hypothesis testing

The null hypothesis H_0, states that there is no difference between the two blood samples at the α= 0.05 level of significance. The alternative hypothesis H_1, states that there is a difference between the two blood samples.

(ii) Decision rule

At the α=0.05 level of significance, the null hypothesis is rejected if $p < \alpha$ where p is the observed significance level. Otherwise, the null hypothesis is accepted at the same level of significance.

PROCEDURE 5 – KRUSKAL-WALLIS H TEST

The Kruskal-Wallis H test was used to compare the subjective findings (i.e. results from the Greene Climacteric Scale questionnaire) with those of the placebo group and with those of a similar study (*The efficacy of ProgestoNat® cream in the treatment of menopausal syndrome*) run concurrently by McTeer (2003).

(i) **Hypothesis testing**

The null hypothesis H_0, states that there is no difference between the groups at the α= 0.05 level of significance. The alternative hypothesis H_1, states that there is a difference between the groups.

(ii) **Decision rule**

At the α=0.05 level of significance, the null hypothesis is rejected if $p < \alpha$ where p is the observed significance level. Otherwise, the null hypothesis is accepted at the same level of significance.

If the null hypothesis is rejected for the Kruskal-Wallis H test, then multiple comparison procedures will be performed.

CHAPTER 4

RESULTS

4.1 INTRODUCTION

This chapter covers the results obtained from the statistical analysis of the data collected from the three groups in the study.

4.2 ADMISSIBILITY OF THE DATA

Only the data collected from this trial was accepted for use in this chapter. The data used for the analysis was collected in the manner discussed in chapter 3.

4.3 BARCHARTS

The following barcharts were constructed to represent the findings of the Greene Climacteric Scale Questionnaire. The barcharts are a visual representation of the means of the results obtained from the questionnaire for group 1 (*Dioscorea villosa*), group 2 (placebo) and group 3 (ProgestoNat®).

The barcharts were constructed using Microsoft PowerPoint for Windows 1997.

Figure 4.1

Barchart comparing the means of the Subjective Data

Symptom Scores for Group 1 (*Dioscorea villosa*)

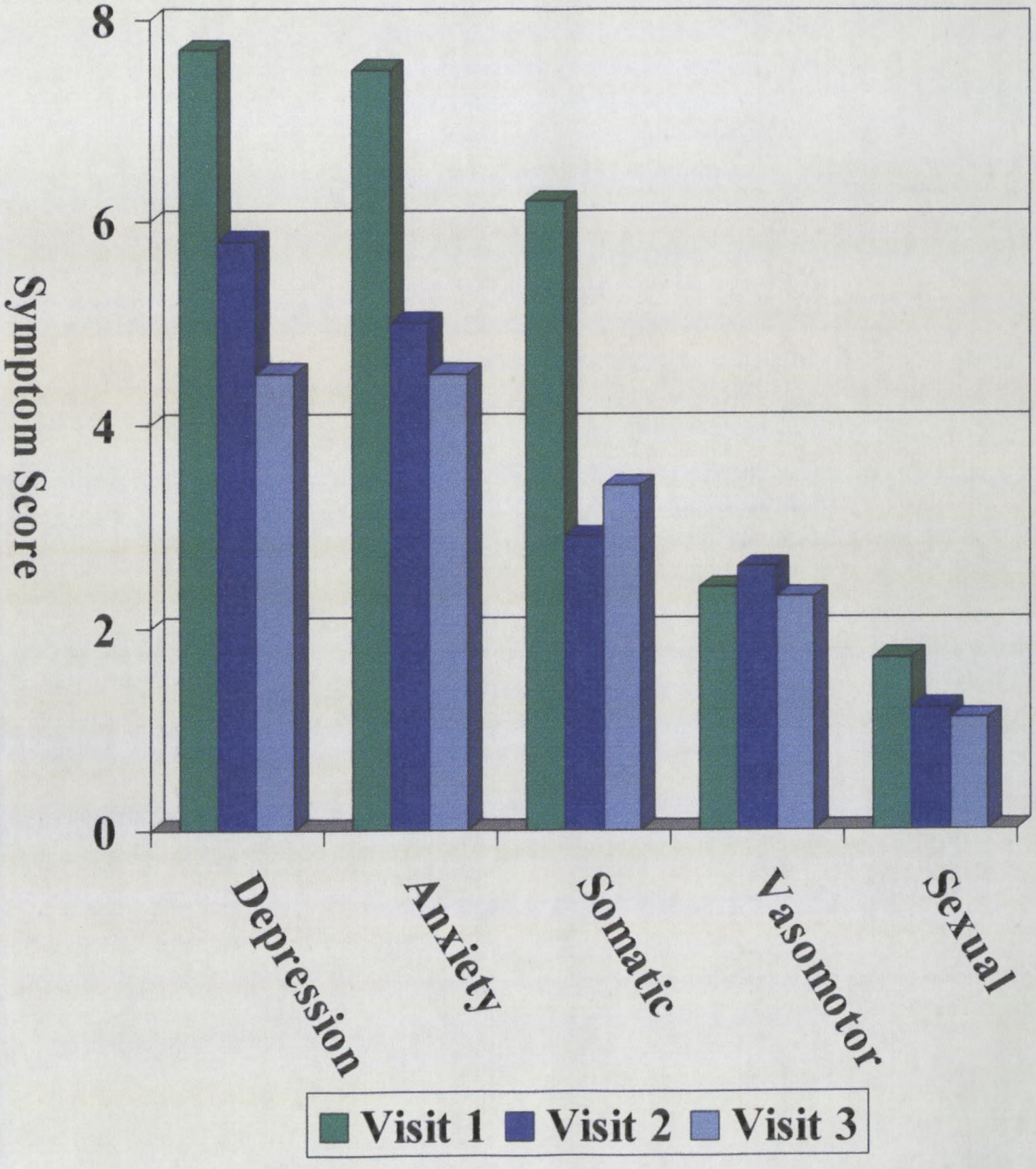


Figure 4.2

Barchart comparing the means of the Subjective Data

Symptom Scores for Group 2 (Placebo)

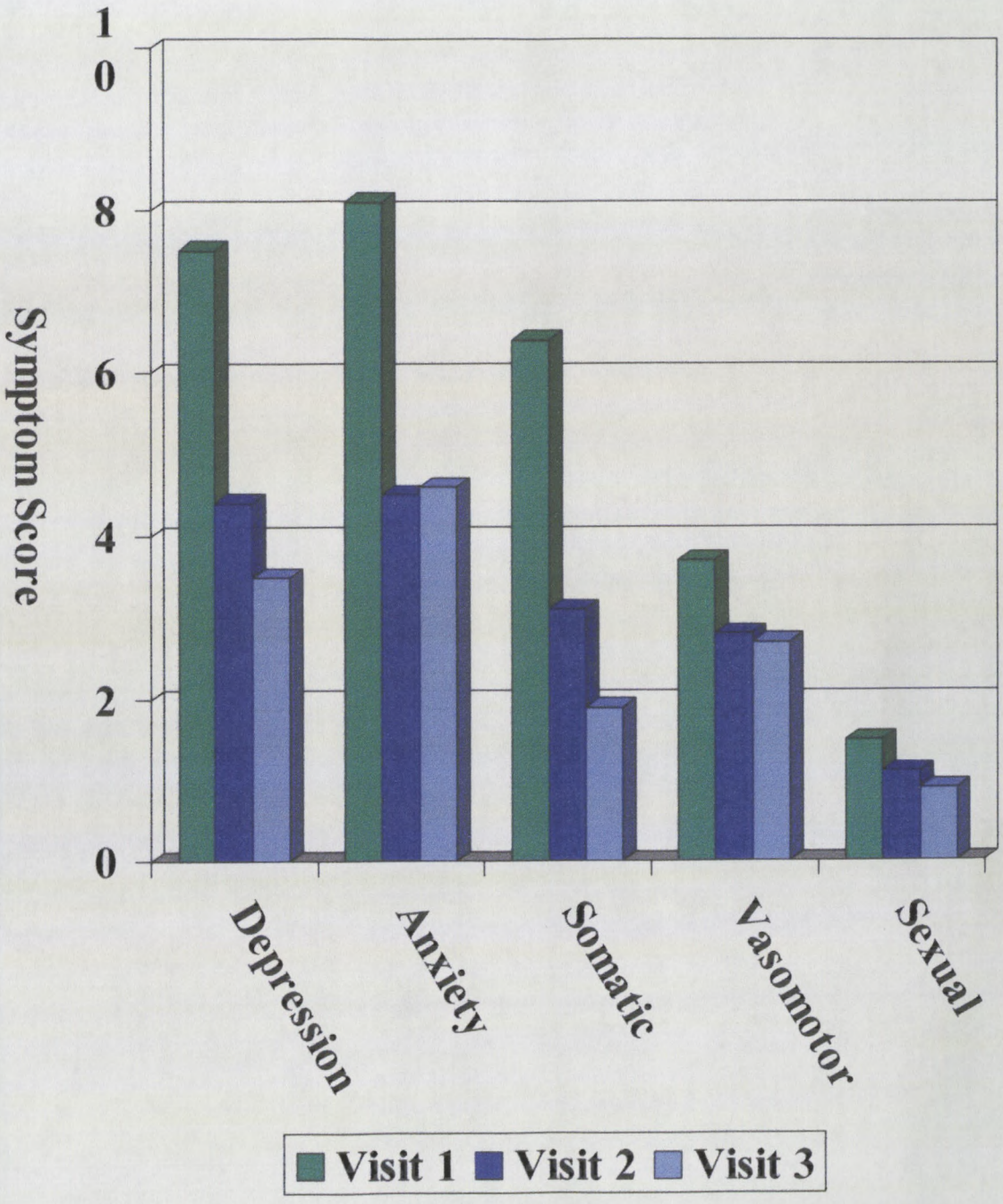
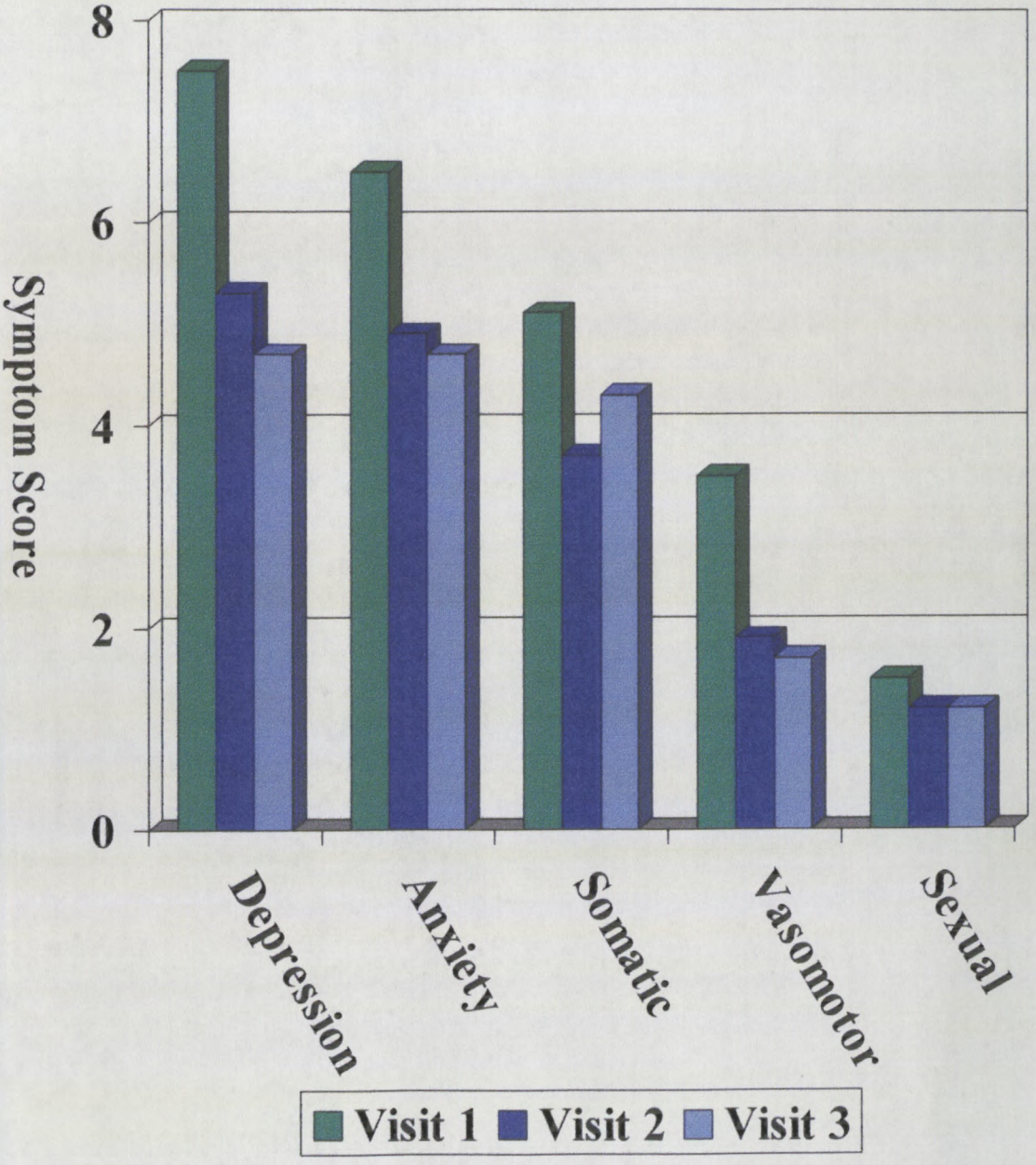


Figure 4.3

Barchart comparing the means of the Subjective Data

Symptom Scores for Group 3 (*ProgestoNat*®)



4.4 PROCEDURE 1 - MANN-WHITNEY U TEST

4.4.1 Inter Group Comparison of the Objective Data for Group 1 (*Dioscorea villosa*) vs Group 2 (Placebo)

Table 4.1

BLOOD TEST	P-VALUE	CONCLUSION
SAMPLE 1	0.065	No difference
SAMPLE 2	0.158	No difference

At the $\alpha = 0.05$ level of significance, the test revealed that there was no statistically significant difference between the two groups for the objective data ($p > 0.05$ – The null hypothesis H_0 was accepted).

4.4.2 Inter Group Comparison of the Subjective Data for Group 1 (*Dioscorea villosa*) vs Group 2 (Placebo)

Table 4.2

SYMPTOM SCORE	P-VALUE			CONCLUSION
	Visit 1	Visit 2	Visit 3	
DEPRESSION	0.851	0.193	0.722	No Differences
ANXIETY	0.477	0.785	0.691	No Differences
SOMATIC	0.690	0.190	0.966	No Differences
VASOMOTOR	0.094	0.703	0.455	No Differences
SEXUAL	0.632	0.680	0.442	No Differences

At the $\alpha = 0.05$ level of significance, the test revealed that there was no statistically significant difference between the two groups for the depression, anxiety, somatic, vasomotor and sexual symptom scores at all three visits ($p > 0.05$ – the null hypothesis H_0 is accepted).

4.5 PROCEDURES 2 & 3- FRIEDMAN'S TEST & DUNN PROCEDURE

4.5.1 Intra Group Comparison of the Subjective Data for Group 1 (*Dioscorea villosa*)

Table 4.3

SYMPTOM	P-VALUE	CONCLUSION
DEPRESSION	0.036	Difference
ANXIETY	0.004	Difference
SOMATIC	0.000	Difference
VASOMOTOR	0.158	No Difference
SEXUAL	0.005	Difference

At the $\alpha = 0.05$ level of significance, the test revealed that there was a statistically significant difference between the visits for depression, anxiety, somatic and sexual symptom scores for group 1 ($p < 0.05$ – The null hypothesis H_0 is rejected). Therefore the Dunn procedure was applied to establish which of the visits were different.

At the $\alpha = 0.05$ level of significance, the test revealed that there was not a statistically significant difference between the visits for the vasomotor symptom scores for group 1 ($p > 0.05$ – The null hypothesis H_0 is accepted).

4.5.1.2 The Dunn Procedure

Since the null hypothesis H_0 was rejected for Friedman's T-test for depression, anxiety, somatic and sexual symptom scores in group 1, the Dunn procedure was applied to determine which of the visits were different.

Table 4.4

		RANK TOTALS
DEPRESSION	VISIT 1	37
	VISIT 2	29.5
	VISIT 3	23.5
ANXIETY	VISIT 1	39.5
	VISIT 2	28.5
	VISIT 3	22
SOMATIC	VISIT 1	42
	VISIT 2	22
	VISIT 3	26
SEXUAL	VISIT 1	37
	VISIT 2	27
	VISIT 3	26

EQUATION: If $|R_j - R_{j'}| \geq z\sqrt{\frac{bk(k+1)}{6}}$, then Rj and Rj' are declared significantly different.

If $\alpha = 0.15$ and k=3, then z=1.96

Therefore $z\sqrt{\frac{bk(k+1)}{6}} = 1.96\sqrt{\frac{15(3)(3+1)}{6}} = 10.73$

Table 4.5

	$R_1 - R_2$	$R_1 - R_3$	$R_2 - R_3$
DEPRESSION	7.5	13.5*	6
ANXIETY	11*	17.5*	6.5
SOMATIC	20*	16*	-4
SEXUAL	10	11*	1

* denotes a significant difference

CONCLUSION:

- There was a statistically significant difference between the first and the third consultations for the depression symptom scores.
- There was a statistically significant difference between the first and the second, and the first and the third consultations for the anxiety symptom scores.
- There was a statistically significant difference between the first and the second, and the first and the third consultations for the somatic symptom scores.
- There was a statistically significant difference between the first and the third consultations for the sexual symptom scores.

4.5.2 Intra Group Comparison of the Subjective Data for Group 2 (Placebo)

Table 4.6

SYMPTOM	P-VALUE	CONCLUSION
DEPRESSION	0.002	Difference
ANXIETY	0.005	Difference
SOMATIC	0.000	Difference
VASOMOTOR	0.477	No Difference
SEXUAL	0.069	No Difference

At the $\alpha = 0.05$ level of significance, the test revealed that there was a statistically significant difference between the visits for depression, anxiety and somatic symptom scores for group 2 ($p < 0.05$ – The null hypothesis H_0 is rejected). Therefore the Dunn procedure was applied to establish which of the visits were different.

At the $\alpha = 0.05$ level of significance, the test revealed that there was not a statistically significant difference between the visits for the vasomotor and sexual symptom score for group 2 ($p > 0.05$ – the null hypothesis H_0 is accepted).

4.5.2.1 The Dunn Procedure

Table 4.7

		RANK TOTALS
DEPRESSION	VISIT 1	40
	VISIT 2	28.5
	VISIT 3	21.5
ANXIETY	VISIT 1	39
	VISIT 2	26.5
	VISIT 3	24.5
SOMATIC	VISIT 1	41.5
	VISIT 2	27.5
	VISIT 3	21

EQUATION: If $|R_j - R_{j'}| \geq z\sqrt{\frac{bk(k+1)}{6}}$, then Rj and Rj' are declared significantly different.

If $\alpha = 0.15$ and k=3, then z=1.96

Therefore $z\sqrt{\frac{bk(k+1)}{6}} = 1.96\sqrt{\frac{15(3)(3+1)}{6}} = 10.73$

Table 4.8

	$R_1 - R_2$	$R_1 - R_3$	$R_2 - R_3$
DEPRESSION	7.5	13.5*	6
ANXIETY	11*	17.5*	6.5
SOMATIC	20*	16*	-4

* denotes a significant difference

CONCLUSION:

- There was a statistically significant difference between the first and the third consultations for the depression symptom scores.
- There was a statistically significant difference between the first and the second, and the first and the third consultations for the anxiety symptom scores.
- There was a statistically significant difference between the first and the second, and the first and the third consultations for the somatic symptom scores.

4.6 PROCEDURE 4 - WILCOXON SIGNED RANK TEST

4.6.1 Intra Group Comparison of the Objective Data for Group 1 (*Dioscorea villosa*)

Table 4.9

BLOOD TEST	P-VALUE	CONCLUSION
Sample 1 vs Sample 2	0.031	Difference

At the $\alpha = 0.05$ level of significance, the test revealed that there was a statistically significant difference between the two blood samples for group 1 ($p < 0.05$ – The null hypothesis H_0 is rejected).

4.6.2 Intra Group Comparison of the Objective Data for Group 2 (Placebo)

Table 4.10

BLOOD TEST	P-VALUE	CONCLUSION
Sample 1 vs Sample 2	0.156	No Difference

At the $\alpha = 0.05$ level of significance, the test revealed that there was not a statistically significant difference between the two blood samples for group 2 ($p > 0.05$ – The null hypothesis H_0 is accepted).

4.5 PROCEDURE 5 - KRUSKAL-WALLIS TEST

Inter Group Comparison of the Subjective Data for Group 1 (*Dioscorea villosa*) vs Group 2 (Placebo) vs Group 3 (ProgestoNat®)

Table 4.11

SYMPTOM SCORE	P-VALUE			CONCLUSION
	Visit 1	Visit 2	Visit 3	
DEPRESSION	0.990	0.458	0.832	No Differences
ANXIETY	0.330	0.926	0.861	No Differences
SOMATIC	0.562	0.403	0.258	No Differences
VASOMOTOR	0.166	0.406	0.383	No Differences
SEXUAL	0.857	0.923	0.634	No Differences

At the $\alpha = 0.05$ level of significance, the test revealed that there was no statistically significant difference between the three groups for the depression, anxiety, somatic, vasomotor and sexual symptom scores at all three visits ($p > 0.05$ – The null hypothesis H_0 is accepted).

CHAPTER 5

DISCUSSION

Conventional treatment for the symptoms experienced during the menopausal transition is hormone replacement therapy (HRT). Although the medical profession has strongly advocated the use of HRT, women are ambivalent about hormonal therapies. Statistics from Europe and the USA indicate that only 10 – 20 % of menopausal women are taking HRT on a regular basis. Among the women who begin to use HRT, less than 40% continue to use it and up to 30% do not get the prescription filled. The low rates of utilisation are due to a number of factors. The most commonly cited reason is the fear of breast cancer. Other issues include the side effects of HRT such as bleeding, weight gain, bloating, cramping and headaches (Taylor, 2001).

Among the alternative treatments available for menopausal symptoms is Mexican wild yam (*Dioscorea villosa*). However, there have been no studies as to the safety or efficacy of wild yam in the management of menopausal symptoms. This chapter attempts to discuss the results of the statistical analyses on the effects of Wild yam in the treatment of menopausal syndrome displayed in chapter 4.

Statistical analysis

The difference between the treatment and placebo groups for the baseline (i.e. first consultation) measurements of both the subjective and objective data is statistically insignificant. This is important, as a statistically significant difference between the two groups would indicate an inappropriate measure of comparison.

Subjective data

The Mann Whitney test was used to evaluate the difference between the treatment and the placebo groups for the subjective data. This test revealed that the differences between the two groups were insignificant. Friedman's test was then used to determine whether there was a difference in the symptom scores between the consultations within each of the groups. This test revealed that there was a statistically significant improvement in the treatment group for the depression ($p=0.036$), anxiety ($p=0.004$), somatic ($p=0.000$) and sexual ($p=0.005$) symptom scores. It also revealed a statistically significant improvement in the placebo group for the depression ($p=0.002$), anxiety ($p=0.005$) and somatic ($p=0.000$) symptom scores.

The depression symptom score on the Greene Climacteric Scale questionnaire is subdivided into the following symptoms: feeling tired or lacking energy, loss of interest in most things, feeling unhappy or depressed, crying spells and irritability. For both the treatment and the placebo groups, the Dunn procedure revealed that there was a statistically significant improvement between the first and the

third consultations for the depression symptom scores. The depression symptom scores improved by 42% in the treatment group and by 53% in the placebo group. There was therefore a greater improvement in depression symptom scores in the placebo group when compared to the treatment group.

The anxiety symptom score on the Greene Climacteric Scale questionnaire is subdivided into the following symptoms: heart beating quickly or strongly, feeling tense or nervous, difficulty in sleeping, excitable, attacks of panic and difficulty in concentrating. For both the treatment and the placebo groups, the Dunn procedure revealed that there was a statistically significant improvement between the first and second consultations as well as between the first and third consultations. The anxiety symptom scores improved by 41% in the treatment group and by 43% in the placebo group. Therefore there was a greater improvement in anxiety symptom scores for the placebo group when compared to the treatment group.

The somatic symptom score on the Greene Climacteric Scale questionnaire is subdivided into the following symptoms: feeling dizzy or faint, pressure or tightness in the head or body, parts of the body feel numb or tingling, headaches, muscle and joint pains, loss of feeling in hands or feet and breathing difficulties. The Dunn procedure revealed that there was a statistically significant difference between the first and second consultations as well as between the first and third consultations for both the treatment and the placebo groups. The somatic

symptom scores improved by 45% in the treatment group and by 70% in the placebo group. Therefore the placebo group showed a greater improvement in somatic symptom scores when compared to the treatment group

The vasomotor symptom scores on the Greene Climacteric Scale questionnaire are subdivided into the following symptoms: hot flushes and sweating at night. Friedman's test showed that the difference between the consultations was insignificant for the vasomotor symptom scores in both the treatment and the placebo groups.

The sexual symptom score on the Greene Climacteric Scale questionnaire consists of only one symptom: loss of sexual interest. The Dunn procedure revealed that there was a statistically significant difference between the first and the third consultation for the sexual symptom scores in the treatment group. The sexual symptom scores improved by 23% in the treatment group. Friedman's test showed that the difference between the consultations for the sexual symptom scores in the placebo group was insignificant.

Although the depression, anxiety and somatic symptom scores showed a statistically significant improvement in the treatment group, the placebo group showed an improvement that was more significant. There is therefore no difference between the treatment and the placebo groups with respect to the subjective symptoms, as revealed by the Mann Whitney test (Table 4.2). The

most immediate explanation for this result is the placebo effect, the fact that the expectation of an effect from an ingested substance or therapeutic transaction can actually produce a bodily effect (Peters, 2001). The act of massaging a cream into the skin is very therapeutic, regardless of whether the cream is medicated or not. However, several other factors could have also played a role in bringing about this response in the placebo group. One possible explanation is the natural course of the condition. Menopausal symptoms change with time and become less prominent as the postmenopausal phase approaches (Voda, 1997). It is possible that the symptoms were first measured at or near their peak, and a second measurement gave a lower reading as a result of the natural progression of the condition. Another explanation could be that the common ingredients that form the cream base (Appendix C) that are present in both the treatment and the placebo creams had a therapeutic effect on the relevant menopausal symptoms. Therefore the placebo cream should more accurately be called a 'pseudoplacebo'; an intervention that is active in principle but not for the condition that is being treated (Peters, 2001).

A further explanation for the response in the placebo group could be the Hawthorne effect. The Hawthorne effect describes the tendency for people to change their behaviour because they are the target of special interest and attention (Peters, 2001). This study was advertised in a major newspaper, through which we received an enormous response from volunteers. The volunteers all met with the researcher at the same time so that the study and its

criteria could be discussed in detail. It was noted by the researcher that the volunteers felt privileged to be a part of this research, the results of which could play a major part in the future of all women. The volunteers spoke amongst each other about their condition and exchanged advice on what they felt helped them. They were therefore the target of special interest and more attention was paid to their condition. Although the participants were encouraged to not alter their lifestyle in any way, it is possible that their attitude and behaviour changed as a result of this attention.

Another possible reason for the improvement of symptom scores could be politeness and experimental subordination. Participants report improvement in order to please the doctor, whereas in fact nothing has improved. Experimental subordination is a phenomenon whereby experiment subjects report what they think is expected of them, rather than what they really experience (Peters, 2001).

Objective data

The Mann Whitney test was used to evaluate the difference between the treatment and the placebo groups with respect to the objective data (i.e. the progesterone measurements). This test revealed that the difference between the two groups was statistically insignificant. Wilcoxon's signed rank test was then used to determine whether there was a difference between the two progesterone measurements within each of the groups. The treatment group showed a

significant difference between the two measurements (p=0.031), however the placebo group showed no difference (p=0.156).

Although the treatment group showed a statistically significant difference between the progesterone measurements, this difference occurred in the reverse direction to that which was expected. I.e. the progesterone measurements decreased as opposed to the expected result of an increase in progesterone levels. One possible reason for this could be the timing during the menstrual cycle that the blood samples were collected. Although the researcher maintained an average of 28 days between the consultations, variations in the menstrual cycles do occur, especially during the menopausal transition. Irregularities in the menstrual cycle are one of the primary symptoms of perimenopause. Another reason for the discrepancy is that the chemical structure of *Dioscorea villosa* is not identical to that of progesterone that occurs naturally in the human body, and therefore it is possible that the Elecsys Progesterone II procedure is not an accurate measurement tool in quantifying levels of progesterone of *Dioscorea villosa* origin. It is the opinion of the researcher that *Dioscorea villosa* may be structurally similar to progesterone and is thus able to attach to the progesterone receptors and act as a competitive agonist (i.e. initiate the same pathways as progesterone). The Elecsys Progesterone II test is a procedure that measures the total progesterone in the blood, and not only the free progesterone levels.

Although the progesterone levels in the blood decreased, there was a simultaneous improvement in the symptoms experienced by the participants. This observation challenges the current thought about the mechanism of action of progesterone creams. The current thought is that the progesterone is absorbed into the blood and negates the state of estrogen dominance, bringing the hormones into balance and thereby relieving the symptoms of menopause (Bond & Rushton, 1999). *Discorea villosa* is not used in its natural form for the treatment of menopausal symptoms as it is not known whether the body is able to make the conversion of *Diosgenin* into a form of progesterone that is recognised by the body. However, it is possible that *Dioscorea villosa* works according to a different method. It is a herb that contains many active substances, including *Diosgenin*, alkaloids and steroidal saponins (Wilmont,1999). Perhaps it acts according to a method that utilises a combination of the active substances that are found naturally in the herb, and not by increasing the progesterone levels in the blood.

Another explanation for the decrease in progesterone levels in the blood with a simultaneous improvement in symptoms could be that *Dioscorea villosa* has progesterone-like qualities. Perhaps it is able to attach to the same receptors as progesterone and initiate the same effects, as discussed earlier. If this is the case, it is possible that the *Dioscorea villosa* that is absorbed into the blood has a negative feedback effect on the anterior pituitary gland. During the normal female sexual cycle, the increase in progesterone in the postovulatory phase

causes a negative feedback effect on the anterior pituitary gland. This inhibits the release of LH and FSH by the anterior pituitary gland. The follicles in the ovaries are therefore no longer stimulated to grow, resulting in a reduction in the production of progesterone by the ovaries. Therefore the progesterone that is measured by the Elecsys Progesterone II test is decreased. However, the progesterone receptors are still being stimulated by the *Dioscorea villosa* that is not detected by the Elecsys Progesterone II test. The *Dioscorea villosa* is therefore negating the state of estrogen dominance, resulting in an improvement in menopausal symptoms. Therefore a more precise study would be to measure progesterone, estrogen, LH and FSH at each of the consultations.

The decrease in progesterone levels could also be due to the natural course of the condition. As discussed in chapter 2, during menopause the ovaries shrink and become less receptive to the effects of FSH and LH. Eventually, with time there are no more follicles left in the ovaries to be stimulated by FSH and LH, and therefore no progesterone is produced by the ovaries (Llewellyn-Jones, 1999). The observed reduction in progesterone with a simultaneous improvement in symptoms could be due to the natural progression of the condition.

Comparison with ProgestoNat ®

The Kruskal-Wallis test was used to assess whether there was a statistically significant difference for the subjective data between group 1 (*Dioscorea villosa*),

group 2 (placebo) and group 3 (ProgestoNat ®). The test revealed that there was no difference between all three groups with respect to the subjective data. This could be due to all three creams containing the same base ingredients (Appendix C), or it could be due to the placebo effect. There is therefore no difference between the efficacy of the test substances *Dioscorea villosa* and ProgestoNat ® in the treatment of menopausal symptoms.

Side-effects

Although there were no side effects experienced by any of the participants in either of the groups, some patients in the treatment group who had been experiencing infrequent and irregular menstruation before commencement of the cream, reported a recurrence of menstrual bleeding. The form of menstrual bleeding ranged from 'spotting' once or twice during the treatment period, to very heavy bleeding. It is the opinion of the researcher that a recurrence in menstrual bleeding should be regarded as a side effect of the treatment cream. Uterine bleeding is also one of the common side-effects of HRT (Hoover & Wallach, 2002). Thus it can be argued that since the treatment group experienced the recurrence of uterine bleeding, *Dioscorea villosa* must have been absorbed into the blood and produced progesterone-like effects.

Limitations of the study

The Greene Climacteric Scale questionnaire was used to subjectively assess the severity of the menopausal symptoms experienced by the participants.

Difficulties arose in assessing some of the symptoms in the questionnaire that are not purely symptoms of menopause, but may be attributed to other conditions. Such an example is the symptom 'parts of the body feel numb and tingling'. This symptom is not restricted to menopause, but may occur as a result of a host of other conditions. The psychological symptoms were also difficult to assess at times, as participants often have other events in their personal lives that impact on their psychological well being and are not only due to hormonal imbalances. Such events include financial difficulties, loss of a job or death of a family member. Thus it is the opinion of the researcher that the Greene Climacteric Scale questionnaire is not an appropriate method for accurately assessing the severity if menopausal symptoms. A more precise questionnaire that only focuses on the exclusive symptoms of menopause would be a more appropriate assessment tool.

Since progesterone levels vary dramatically throughout the phases of the menstrual cycle, it is important that blood samples are drawn at the same time of the menstrual cycle for each of the participants in order to ensure standardisation. An effort was made to overcome this difficulty by holding each of the three consultations between the first and the third day of the menstrual cycle. However, since menstrual irregularity is one of the symptoms of perimenopause, this was difficult to maintain. As a result, it is the opinion of the researcher that the progesterone measurements are not as accurate as they could be. It would be more accurate if a minimum of three progesterone

measurements were taken during the treatment period. However, due to financial constraints more progesterone tests were not possible for this study.

The base ingredients (appendix C) in the treatment and placebo creams were used in order to create uniformity with the ProgestoNat® cream. Since the base substances were included in the ProgestoNat® cream, they were also included in the *Dioscorea villosa* and placebo creams, so that the only differences between the creams were the active ingredients. I.e. Natural progesterone in the ProgestoNat® creams, *Dioscorea villosa* in the *Dioscorea villosa* creams and no active ingredient in the placebo creams. However, the addition of the base substances proved to be a disadvantage. This is because it was impossible to distinguish between whether the improvements that were observed were due to the test substances or due to the base substances. This posed as a difficulty because improvements were observed in the subjective symptoms for all three groups.

The aim of this study was to determine the efficacy of *Dioscorea villosa* cream in the treatment of menopausal syndrome. This study did not attempt to determine the effectiveness of *Dioscorea villosa* in the prevention or treatment of the long-term effects of menopause (i.e. osteoporosis, cardiovascular disease and alzheimer's disease). A follow up period of at least five years would be required for this assessment.

CHAPTER 6

CONCLUSIONS AND RECOMMENDATIONS

6.1 CONCLUSIONS

The first objective of this study was to determine the efficacy of *Dioscorea villosa* cream in the treatment of menopausal syndrome in terms of subjective data. The Greene Climacteric Scale questionnaire was used for this purpose. Inter group comparison procedures revealed that there was no difference between the treatment group and the placebo group with respect to the symptom scores obtained from the questionnaire. Intra group comparison procedures (i.e. within each of the groups) displayed a significant improvement in the depression, anxiety, somatic and sexual symptom scores within the treatment group. The depression, anxiety and somatic symptom scores improved significantly within the placebo group. Therefore, although there were significant improvements in the treatment group, similar improvements were observed in the placebo group. This could be due to the common base ingredients that were present in both the treatment and the placebo creams, or it could be due to the placebo effect. Other reasons were discussed in the previous chapter. Although there was not a statistically significant difference between the two groups, the notable improvements within each of the groups cannot be ignored.

The second objective of this study was to determine the efficacy of *Dioscorea villosa* cream in the treatment of menopausal syndrome in terms of objective data. The objective data consisted of blood progesterone measurements before and after the treatment period. It was expected that the cream would cause an increase in the blood progesterone levels. However, it was observed that the blood progesterone measurements decreased significantly in the treatment group and no difference was observed within the placebo group. The decrease in the blood progesterone levels occurred with a simultaneous improvement in the subjective data. This observation challenges the current thought on the method of action of natural progesterone creams. Although the difference between the two groups with respect to the objective data was not significant, the observations are nevertheless interesting.

The third objective of this study was to compare the efficacy of *Dioscorea villosa* cream with that of *ProgestoNat* ® cream (McTeer, 2003) in terms of the subjective data gathered in these two studies. It was concluded that there was no difference between the efficacy of these two treatments in terms of the subjective data.

6.2 RECOMMENDATIONS

The following recommendations should be considered for future studies of this nature:

- The treatment creams should contain only the substance that is being tested and no base ingredients. The placebo cream should therefore be an aqueous cream with no base ingredients.
- In order to assess the subjective data, a more simplified questionnaire should be used that only contains the exclusive symptoms of menopausal syndrome.
- In order to avoid discrepancies in the blood progesterone measurements (in terms of the timing in the menstrual cycle that the blood samples are drawn), a minimum of three blood samples should be drawn from each participant, one at each of the consultations.
- More comprehensive tests should be performed at all the consultations that include progesterone, estrogen, LH and FSH measurements.
- *In vitro* studies should be performed to determine whether the Elecsys Progesterone II test is an appropriate measurement tool in quantifying levels of progesterone of *Dioscorea villosa* origin.
- For the assessment of the absorption of the cream, saliva tests could be used that are less invasive for the participants (Bond & Rushton, 1999).
- Monitoring of the subjective symptoms should occur more frequently, and not only once a month.

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APPENDIX A

INFORMATION WITH REGARDS TO RESEARCH PROJECT

TITLE OF RESEARCH PROJECT:
The efficacy of *Dioscorea villosa* and *ProgestoNat* ® creams in the treatment of menopausal syndrome.

NAME OF SUPERVISOR:
Dr David Naude M.Tech (Hom) (TN)

NAME OF RESEARCH STUDENTS:
Louise Macquet-Maurel
Taryn McTeer

Dear Patient,

The aim of this study is to evaluate the effectiveness of *Dioscorea villosa* (Wild yam) and *ProgestoNat* ® creams in the treatment of menopausal syndrome.

Forty-five people will be required to complete this study. Each participant will be randomly allocated to one of three equal groups. The selection criteria requires that patients be between 40 – 55 years of age and currently experiencing at least two major and one minor of the following symptoms:

Major symptoms:
- Hot flushes
- Menstrual irregularities
- Dry vaginal canal / painful intercourse
- Irritability and mood changes

Minor symptoms:
- Headaches
- Poor bladder control
- Memory loss
- Loss of libido
- Ringing in the ears
- Bleeding gums

Patients who fall into any of the following categories will be excluded from the study:
- Patients who are on hormone replacement therapy (HRT) or any other treatment (including herbal remedies) for menopausal symptoms.
- Patients experiencing premature menopause or any other condition in which estrogen production is deficient.

- Patients who have had a total hysterectomy.
- Patients who are on other medication such as thyroxin, psychotropic drugs or coticosteroids which may affect the presentation of menopausal symptoms.

Each group will receive a different treatment in order to determine which treatment is more effective. One group will receive a cream containing *Dioscorea villosa* tincture. Another group will receive *ProgestoNat* ® cream, which contains *Diosgenin*, also referred to as 'natural' progesterone. The last group will receive a control cream. This is a cream that is unmedicated, but indistinguishable from the other creams. All three creams will contain the following added ingredients:

- *Aloe vera*
- Borage oil
- *Calendula officinalis* (Marigold)
- *Echinacea angustifolia*
- *Evening primrose oil*
- *Piper methysticum* (Kava Kava)
- *Symphytum officinale* (Comfrey)
- Vitamin E

Benefits of the study:

The benefit of this study is that the participants in the treatment groups will be given free treatment for their symptoms of menopausal syndrome. The control group will be given the option of free treatment at the end of the study. There will also be an opportunity to increase their knowledge of menopause.

Remuneration:

No remuneration will be offered to participants of this study.

Procedure of the study:

Each participant will be required to attend three consultations with the researcher. During each consultation the patient will fill in a questionnaire regarding the symptoms they are experiencing. A blood sample will be taken by a registered nurse at the beginning of the study, and again at the end of the study. The progesterone level in the blood will be measured. No other tests will be performed on the blood sample. The results of the blood tests will be made available to the patients. Each consultation will take place on day 1 – 3 of the menstrual cycle (ie. The first to the third day of the start of menstrual bleeding). If menstruation does not occur, the following consultation will be held on day 35 of the menstrual cycle. The length of the study will be 2 cycles. At the end of the study the questionnaires and blood test results will be compared and analysed to ascertain which treatment provides the best results.

Confidentiality:

All the results are confidential and will only be viewed by the researcher, and supervisor.

Risks and Discomfort:

Complications are not expected from either of the treatments nor the control, however you have the option of withdrawing from the study without motivation. The only slight discomfort experienced may be that of acquiring the blood sample, however this will be performed by a registered nurse according to stringent safety protocol.

You are kindly asked not to alter your lifestyle in any way for the duration of the study and to refrain from using any other form of treatment for the symptoms you are experiencing, as this may alter the outcome of treatment and thus the results of the study. You are free to treat any unrelated conditions accordingly, but please inform the researcher if this occurs.

The treatment is supervised by a qualified homoeopath and is free of charge. In case of any queries or problems that may arise during the study, please contact:

Louise Macquet-Maurel Tel: 0837826462
Taryn McTeer Tel: 0836616286
Dr David Naude Tel: 2042041 (Durban Institute of Technology)

Thank-you for your participation in this study

Kind Regards
Louise Macquet-Maurel and Taryn McTeer
(Final year homoeopathy students)

Patient Name: _____ Signature: _____
(in block letters)

Witness Name: _____ Signature: _____
(in block letters)

IMININGWANE YOPHANDO OLWENZIWAYO

ISIHLOKO SOPHANDO OLWENZIWAYO:
Ukusebenza kwe *Dioscorea villosa* ne *ProgestoNat* ® imithi esetshenzisela ukwelapha kokuvaleka kokuya esikhathini.

IGAMA LOMQEQESHI UMSIZI:
Dr David Naude M.Tech (Hom) (TN)

IGAMA LOMFUNDI OPHANDAYO:
Louise Macquet-Maurel
Taryn McTeer

Siguli Esithandekayo,

Injongo yaloluphando ukuthola ukusebenza kahle komithi obizwa ngokuthi *iDioscorea villosa* ne *ProgestoNat* ® okuwu khilimu abalwa nokuvaleka kokuya esikhathini.

Kuyodingeka abantu abangamashumi amane nanhlanu ukwenza loluphando. Ilowo nalowo oyobamba iqhaza uyofakwa ngokungakhethiwe kwelinye lamaqoqo amathathu alinganayo. Indlela okukhethwe ngayo ifuna ukuba iziguli zibe neminyaka ephakathi kwamashumi amane nanhlanu kuya emashumini amahlanu nanhlanu ubudala abakhombisa okungenani izinkomba ezimbili ezinkulu nenkomba eyodwa yalokhu okulandelayo:

Izinkomba ezinkulu:
- Ukuzwela ukushisa nokujuluka kungashisi
- Ukuya esikhathini ngendlela engamukelekile
- Ukoma ngaphanzi / nobuhlungu uma uya ocansini
- Ukushesha ukucasuka nokungahlali ujabulile

Izinkomba ezincane:
- Ukuphathwa ikhanda
- Ukuhluleka ukubamba umchamo
- Ukukhohlwa
- Ukungalangazeleli ukuya ocansini
- Izindlebe ezidumayo
- Izinsini ezophayo

Iziguli ezingena kuloluhla olulandelayo ziyosuswa zingabe zisaba ingxenye yaloluphando:
- Iziguli vele esezelashelwa khona ukuvaleka
- Iziguli ezizithola zivaleka ngaphambi kwesikhathi
- Iziguli esezakhishwa isibeletho
- Iziguli ezelashelwa ezinye izifo

Ilelo naleloqoqo liyonikezwa ukwelashwa okwahlukile khona kuzobonakala ukuthi iyiphi indlela eyelapha ukwedlula enye. Iqoqo lokuqala liyonikezwa ukhilimu ofakwe iDioscorea villosa. Iqoqo lesibili liyonikezwa ukhilimu iProgestoNat ® one Diosgenin. Iqoqo lesithathu lithole ukhilimu ongenamuthi kodwa ongeke ukwazi okulehlukanisa kuneminye one placebo kuphela. Bobathathu labokhilimu bayoba nalezithako ezilandelayo:

- *Aloe vera*
- *Borage oil*
- *Calendula officinalis* (Marigold)
- *Echinacea angustifolia*
- *Evening primrose oil*
- *Piper methysticum* (Kava kava)
- *Symphytum officinale* (Comfrey)
- Vitamin E

Imiphumela yalokukuhlolwa:

Imiphumela yalokukuhlolwa ukuthi zonke iziguli ezibambe iqhaza kuloluphando zithole ukwelashwa mahlala izinkomba zokuvaleka kokuya esikhathini. Iqoqo lokugcina lona liyonikwa ithuba lokuzikhethela ukuthi liyafuna yini ukwelashwa ekupheleni kophando. Bayothola futhi ithuba lokwazi kabanzi ngokuvaleka kokuya esikhathini.

Ukukhokheleka:

Bonke abathathe iqhaza kuloluphando angeke bakhokhelwe.

Indlela okuyoqhutshwa ngayo:

Ilowo nalowo oyobamba iqhaza kuloluphando, kuyomele abonane nomphandi izihlandla ezintathu. Kuleso nalesosikhathi bebonana, isiguli kuyomele sigcwalise siphendule imibuzo ngezinkomba ezizibonayo nezizizwayo. Umhlengikazi oqeqeshiwe uyothatha igazi kuleso nalesosiguli ngaphambi kokubamba iqhaza kulolucutshungulo kanjalo futhi noma seluphelile. Izinga le progesterone egazini liyokalwa. Akukho okunye ukuhlolwa okuyokwenziwa egazini elithathiwe. Ukubonana kwesiguli nomcubonguli kuyokwenzeka njalo osukwini lokuqala kuya kwelesithatho sokuya esikhathini kuleyonyanga. Ubude bokuhlolwa kuyokuba izinyanga ezimbili. Ekupheleni kokuhlolwa konke okuyobe kusetsenziswa kuyobe sekuqhathaniswa kulutshungulwe ukuze kutholakale ukuthi iliphi ikhambi elisebenza kahle uma kuqhathaniswa lawa amathathu.

Ubumfihlo:

Yonke imiphumela eyotholakala iyoba imfihlo futhi iyobonwa kuphela ilowo ocubulungayo kanjalo nalowo omsizayo.

Ubucayi nokungakhululeki:

Abukho ubungozi obuyotholakala ngokusebenzisa noma iliphi elinye lalamakhambi kodwa isiguli sivumelekile ukuhoxa ekubeni ingxenye yaloluphando ngaphandle kokunikeza isizathu. Okuyikhona kungakhululeki okuyozwiwa iziguli ilokho kokuthatha igazi kodwa lokho kuyokwenziwa umhlengikazi oqeqeshiwe futhi oyoqiniseka ukuthi usebenzisa izinto ezifanele ukwenza lokho futhi esebenzisa izinto ezihlanzekile.

Uyacelwa ukuthi ungashintshi indlela yakho yokuphila ngesikhathi kwenziwa loluphando futhi kungabibikho mithi oyisebenzisayo okwalesikhathi njengoba ukwenza njalo kungakhinyabeza imiphumela yalokukuhlolwa. Uvumelekile ukwelapha olunye uhlobo lwesifo ongazithola usunaso inqobo nje uma kungesiso lesi okuohandwa ngaso kodwa futhi kufanele wazise umphandi ngalesosimo.

Ukwelashwa kuzobe kubhekwe kabanzi umuntu oqeqeshwe kabanzi kulomkhakha kanti futhi kumahala. Uma kwenzeka ufuna incazelo noma ufisa ukwanzi kabanzi ngesikhathi luqhubeka uphando, ukhululekiwe ekutheni uxhumane nalaba abalandelo:

Louise Macquet-Maurel	Tel: 0837826462
Taryn McTeer	Tel: 0836616286
Dr David Naude	Tel: 2042041 (Durban Institute of Technology)

Siyabonga ukubamba iqhaza kwakho kuloluphando.

Ozithobayo
Louise Macquet-Maurel and Taryn McTeer
(Final year homoeopathy students)

Igama Lesiguli: _____ Isignature: _____
(Bhala ngamagama amakhulu)

Igama Lofakazi: _____ Isignature: _____
(Bhala ngamagama amakhulu)

APPENDIX B

INFORMED CONSENT FORM

TITLE OF RESEARCH PROJECT:
The efficacy of *Dioscorea villosa* and *ProgestoNat*® cream in the treatment of menopausal syndrome.

NAME OF SUPERVISOR:
Dr David Naude M.Tech(Hom)(TN)

NAME OF RESEARCH STUDENTS:
Louise Macquet-Maurel
Taryn McTeer

DATE: _____

PLEASE CIRCLE THE APPROPRIATE ANSWERS:

1. Have you read the research information sheet? YES/NO
2. Have you had the opportunity to ask questions regarding the study? YES/NO
3. Have you received satisfactory answers to your questions? YES/NO
4. Have you received enough information about this study? YES/NO
5. Do you agree not to discuss any of the particulars of your treatment with any other study participants? YES/NO
6. Who have you spoken to with regards to this study?
   _____.
7. Do you fully understand the implications of your involvement In this study? YES/NO
8. Do you understand that you are free to withdraw from this study:
   1. At any time
   2. Without having to give reason for withdrawing, and
   3. Without affecting your future health care? YES/NO
9. Do you agree to voluntarily participate in this study? YES/NO

If you have answered no to any of the above, please obtain the information before signing

Patient name: _____ Signature: _____
(In block letters)

Witness name: _____ Signature: _____
(In block letters)

Research Sudent name: _____ Signature: _____

ISIHLOKO SOPHANDO OLWENZIWAYO:
Ukusebenza kwe *Dioscorea villosa* ne *ProgestoNat* ® imithi esetshenzisela ukwelapha kokuvaleka kokuya esikhathini.

IGAMA LOMQEQESHI UMSIZI:
Dr David Naude M.Tech (Hom) (TN)

IGAMA LOMFUNDI OPHANDAYO:
Louise Macquet-Maurel
Taryn McTeer

USUKU: _____

Kokolozela izimpendulo ezifanelo:

1. Kungabe ulifundile iphepha locwaningo? YEBO/CHA
2. Kungabe ulitholile ithuba lokubuza imibuzo ngalolucwaningo? YEBO/CHA
3. Kungabe ugculisekile ngezimpendulo ozitholile? YEBO/CHA
4. Kungabe ulutholile ulwazi olwenele ngalolucwaningo? YEBO/CHA
5. Kungabe oyavuma ukungadingidi imininingwane emayelana nokwelashwa nabanye ababambe iqhaza kulolucwaningo? YEBO/CHA
6. Ubani osukhulume naye maqondana nalolucwaningo?
   _____.
7. Uyayiqondisisa imibandela yokuthatha inxaxheba kuloluphando? YEBO/CHA
8. Kungabe uyazi ukuthi ukhululekile ekuhoxeni kuloluphando:
   1. Noma nini
   2. Ngaphandle kokunikeza isizatho.
   3. Ngaphandle kokuba nomthalela ekulashweni kwakho? YEBO/CHA
9. Kungabe uyavuma ukuba ingxenye yaloluphando ngokuthanda kwakho? YEBO/CHA

Uma uphendule ngokuthi cha kwe minye yalemibuzu engenhla, uyacelwa ukuba uthola ulwazi ngaphambi kokusayina.

Igama lesiguli: _____ Isignature:_____
(Bhala ngamagama amakhulu)

Igama lofakazi: _____ Isignature: _____
(Bhala ngamagama amakhulu)

Igama lomfundi ocwaningayo: _____Isignature: _____

APPENDIX C

CONTENTS OF CREAM

Aloe vera 1%	-	Anti-inflammatory and anti-irritant effect on the Skin.
Borage oil	-	A rich source of omega-3 fatty acids.
Calendula officinalis D2	-	Antiseptic, antifugal and anti-inflammatory effect on the skin.
Echinacea angustifolia D2	-	Used topically to treat tired, stressed skin.
Evening primrose oil	-	A rich source of omega-3 fatty acids. Relieves symptoms of premenstrual syndrome and breast pain.
Piper methysticum D2	-	Soothes skin and relieves tension and anxiety.
Symphytum officinale D2	-	Promotes healthy growth of skin cells and healing of skin blemishes. Improves tone and texture of skin.
Vitamin E 1%	-	Has anti-oxidant, free radical scavenging and anti-aging properties.

This Appendix is not intended for Subjects. The contents of the cream are included in the information letter – Appendix A.

APPENDIX D

THE GREENE CLIMACTERIC SCALE (Greene, 1998)

NAME: ..... DATE: .....

NUMBER: .....

Please indicate the extent to which you are bothered at the moment by any of these symptoms by placing a tick in the appropriate box.

SYMPTOMS	Not at all	A little	Quite a bit	Extremely	Score 0-3
1. Heart beating quickly or strongly					
2. Feeling tense or nervous					
3. Difficulty in sleeping					
4. Excitable					
5. Attacks of panic					
6. Difficulty in concentrating					
7. Feeling tired or lacking energy					
8. Loss of interest in most things					
9. Feeling unhappy or depressed					
10. Crying spells					
11. Irritability					
12. Feeling dizzy or faint					
13. Pressure or tightness in head or body					
14. Parts of body feel numb or tingling					
15. Headaches					
16. Muscle and joint pains					
17. Loss of feeling in hands or feet					
18. Breathing difficulties					
19. Hot flushes					
20. Sweating at night					
21. Loss of sexual interest					

Psychological (1-11) = _____ Somatic (21) = _____

Depression (7-11) = _____ Vasomotor (19-20) = _____

Anxiety (1-6)= _____ Sexual (21) = _____

THE GREENE CLIMACTERIC SCALE (Greene, 1998)

IGAMA: ..... USUKU: .....

NUMBER: .....

Uyacelwa ukuthi usho izinga elikuhluphayo okwamanje mayelana nalezinkomba ezilandelayo ngokufaka uphawo esikhaleni esifanele.

Izinkomba	Akukho nhlobo	Kukhona kancane	Kukhona kakhudlwana	Kakhulu	Umphumela 0-3
1. Inhliziyo eshaya ngamandla noma kakhulu					
2. Ukuzizwa ungakhululekile					
3. Ukuba nokunzima ekulaleni					
4. Ukujabula kakhulu					
5. Ukwesaba					
6. Ukungakwazi ukulalelisisa					
7. Ukuzizwa ukhathele					
8. Ukuzithola ungajatshuliswa izinto eziningi					
9. Ukuzizwa udangele					
10. Ukuzizwa unomunyu kuthi khala					
11. Ukushesha ukucasuka					
12. Ukuzizwa unenzululwane noma ukuguleka					
13. Ikhanda noma umzimba oqinile					
14. Ukudikiza nokungawezwa amanye amalunga omzimba					
15. Ukuphathwa ikhanda					
16. Imisipha namalunga omzimba abuhlungu					
17. Izandla nezinyawo eziphelelwe imizwa					
18. Ukuba nobunzima bokuphefumula					
19. Ukushiselwa					
20. Ukujuluka ebusuku					
21. Ukulahlekelwa uthando lokuya ocansini					

Psychological (1-11) = _____ Somatic (21) = _____

Depression (7-11) = _____ Vasomotor (19-20) = _____

Anxiety (1-6)= _____ Sexual (21) = _____

APPENDIX E

METHOD OF MANUFACTURE OF AQUEOUS CREAM

MATERIALS:

Emulsifying Ointment	300g
Phenoxyethanol	10g
Purified water, freshly boiled and cooled, Sufficient to produce	1000g

METHOD:

The Phenoxyethanol was dissolved in sufficient purified water at about 60°C to produce a total weight of about 700g. The emulsifying ointment was melted, and the phenoxyethanol solution was added when both were at about 60°C, and mixed. The cream was gently stirred until cool and sufficient purified water was added to produce 1000g, and mixed (British Pharmacopoeia, 1999).

Dioscorea villosa mother tincture was then added to the aqueous cream at 2% volume to volume, using a secondary emulsifier to facilitate the incorporation. The incorporation was performed at a temperature of 45°C. The following ingredients were then added at 1% volume to volume: *Aloe vera*, *Calendula officinalis*, *Echinacea angustifolia*, *evening primrose oil*, *Piper methysticum*, *Symphytum officinale* and Vitamin E. *Borage oil* was added at 3% volume to volume.