Menopausal Transition: Psychosocial Aspects and the Role of Melatonin in Psychogenic Symptoms

Ruth-Angela Bliss

Being a thesis submitted as
the requirement for the degree of
Doctor of Philosophy
School of Psychology
Faculty of Arts
Victoria University, Melbourne, Australia

March, 2005

ABSTRACT

Psychogenic symptoms (trouble sleeping, lack of energy, difficulty in concentration, nervous tension, feelings of sadness/ downheartedness) are among the most frequently reported symptoms of menopausal transition, as are nocturnal hot flushes/sweats. Few studies have combined psychosocial and biomedical models to seek an explanation as to why menopausal symptoms such as these are problematic for some but not all women during menopausal transitional. In Study 1, 71 transitional women (mean age: 50.02 years, SD: 3.52 years) completed questionnaires examining the predictive value of a number of psychosocial factors in terms of the impact of menopausal symptoms on the ability to maintain a normal lifestyle during transition. Participants included women undergoing natural transition and those using hormone replacement therapy (HRT). A sub-set of participants (N=22) with the highest and lowest psychogenic symptom frequency scores took part in Study 2. Their evening on-set salivary melatonin secretion levels

were compared, as was their exposure to natural light at 500, 3,000 and 10,000 lux levels, their subjective and objective (wrist actigraph) sleep quality and their nocturnal peripheral body temperatures (PBT). Results from Study 1 indicated that, while the quality and availability of health care was of most concern to all participants, domestic environment, including quality of relationships and communications, was the main predictor of successful transition when assessed as the ability to maintain a normal lifestyle during transition. No significant differences were found between natural or HRT-assisted transition in terms of the impact of symptom severity, or the predictive value of psychosocial factors. Participants with low psychogenic frequency scores (less frequent symptoms) showed a trend towards higher evening on-set melatonin secretion levels, and had significantly greater exposure to natural light than their high psychogenic frequency counterparts. These results were consistent regardless of transitional status (natural or HRT-assisted). No significant differences between the high and low psychogenic symptom groups were found in either subjective or objective sleep quality. However, women with high psychogenic frequencies spent significantly more hours with higher peripheral body temperatures (35º - 36ºC) and reported significantly more nocturnal hot flush/sweat episodes than their low psychogenic frequency counterparts. These results show that, in terms of overall menopausal transition, domestic environment plays a major role in the way in which transitional women are able to deal with the

impact of menopausal symptoms during transition. They also suggest a permissive link between melatonin evening on-set of rhythms and psychogenic symptoms that may be mediated by exposure to natural light. However, these results should not be viewed in isolation from each other, but in combination with each other. It could be argued that a healthy domestic environment may affect the perception of symptom severity. This could result in greater involvement in domestic and social activities outside the home, increasing exposure to natural light, and thus better entrained melatonin secretion on-set rhythms. However, any inference of causation (rather than association) requires experimental verification, preferably in research designs where key factors, such as exposure to natural light, can be experimentally manipulated.

ACKNOWLEDGEMENTS

In any long-term research project such as a PhD there are many people who help in there own quiet ways. So, to all my non-university friends and to fellow PhD students, thank you for the many small ways you helped me complete this project. To my adult daughters Selina and Lisia, thanks for stopping me when, in frustration with myself, I determined to commit the whole project to the infamous 'bin 13'. To my son Matthew, who was an 11 year old child when I started my PhD and who is now a tall 16 year old teenager. My love and thanks for living the whole experience with me.

My sincere thanks to my supervisor at Victoria University, Professor Dorothy Bruck. Without her insight, encouragement, and perceptive remarks this project could not have reached fruition. To the Victoria University Faculty of Arts Research Committee members and the staff of the Victoria University Postgraduate Study Unit, your on-going support and help have been greatly

appreciated. At the School of Psychological Sciences, La Trobe University, my thanks to Emma Gould for sharing information on saliva testing, and to Agnes Hazi for her expertise and help in performing the RIA testing. To Cameron van den Heuvel at the University of South Australia, my thanks for your invaluable help with regard to melatonin testing schedules. To Janet Guthrie, Project Leader of the Melbourne Women's Mid-Life Health Project for allowing me to use their 33-item health symptom checklist for my own research purposes. To Jo Wainer, herself a noted academic, who kindly allowed me to use her quotations on menopausal transition in this thesis.

To Rick Rushton, who five years ago was merely a contact name at Mini Mitter Inc. in Bend, Oregan. My love and thanks, not only for all your helpful advice regarding physiological data monitoring devices, but also for the enduring friendship that has developed between your family and mine.

To all the menopausal women who took part in this study knowing the results would not necessarily benefit their own transition, but hoping they would benefit the transition of those to come – thank you so much for your support throughout this research study.

TABLE OF CONTENTS

LIST OF TABLES

Table **Page**

LIST OF FIGURES

Figure **Page**

APPENDICES

Chapter

STATEMENT OF RESEARCH

Many studies of symptoms of menopausal transition indicate that the most frequently reported symptomatic problems during transition are:

(i) poor sleep quality, including sleep fragmentation and the occurrence of nocturnal flushes and/or sweats;

(ii) general mood disturbances, ranging in intensity from mild feelings of sadness and downheartedness to severe depression.

However, research has shown that not all women who self-report such symptoms see them as debilitating in terms of maintenance of their pre-transitional lifestyle.

Biomedical researchers have looked to physiological explanations to account for such symptoms, while social and health psychologists have focused on how social and environmental aspects of life impact on the general well-being of transitional women. This diversity of viewpoint has led to some argument as to whether menopausal symptoms should be viewed in isolation, as either hormonal or psychosocial in origin. However, some researchers have recommended that research into menopausal transition must take account of *both* biomedical and psychosocial models when assessing issues dealing with health and ill-health during transition.

The author believes that both psychosocial and biomedical models play an important role in understanding menopausal transition, and should not be viewed in isolation from each other. Not too many years ago, psychological research argued for either a 'nature' or a 'nurture' approach when looking at issues of child development. Today, psychological research into child development acknowledges the combined role of both genetic and environmental aspects. Similarly, the hormonal explanations for menopausal symptoms should not be viewed in isolation from the psychosocial aspects of

transitional women's lives. This research study combines a psychosocial model (Study 1) and a biomedical model (Study 2). It should be noted that the language used to discuss the biomedical model has, by necessity, differed from the language used to discuss the psychosocial model.

To date, most psychosocial studies of menopausal transition have concentrated on defining symptoms encountered, or on investigating the effects, frequencies and/or intensities of specific symptom clusters. Little research has concentrated on the predictive effect of life variables in relation to lifestyle, during this transitional period. Thus, the first stage of this research (Study 1) explored the effects of a wide range of menopausal symptoms on the maintenance of lifestyle during transition. Using questionnaire-based research, a number of life variables were examined in terms of:

(i) their predictive value on overall menopausal symptom severity; and

(ii) their predictive value in terms of psychogenic and nocturnal thermoregulatory symptoms.

Using a sub-set of participants from Study 1, Study 2 investigated the role of melatonin in relation to the psychogenic symptoms of menopausal

transition. Melatonin is the primary endocrinal hormone of the pineal gland. An exhaustive literature review (Medline, Psych Lit, etc) found that no published study that had investigated the role of melatonin secretion levels and/or rhythms within a specifically menopausal transition population. In addition, Study 2 monitored the objective sleep quality and peripheral body temperatures of participants to assess the relationship between psychogenic health and sleep quality, including nocturnal hot flushes/sweats.

There has been much discussion within the menopausal research literature regarding the role of Hormone Replacement Therapy (HRT) during menopausal transition. This study also sought to establish whether results obtained in terms of psychosocial factors and melatonin secretion levels and/or rhythms were impacted upon by the method of transition (natural/HRT-assisted) chosen by its participants.

Participants in this research were all healthy mid-aged women who were not, or had not suffered from any major depressive episodes attributed to their menopausal transition. While Study 1 was questionnaire-based, Study 2 was designed as an exploratory, naturalistic study. Data on salivary melatonin levels, exposure to light, nocturnal peripheral body temperature and quality of sleep were collected as participants went about their normal weekend Saturday activities.

Study 1, which addressed the research question of the predictive affects of menopausal symptoms on lifestyle, and Study 2, which addressed the role played by melatonin in psychogenic symptoms have been written up as two specific research studies. Both studies have their own literature reviews, methodologies and results chapters. However, the discussion chapter integrates the results from both studies.

CHAPTER 1

MENOPAUSAL TRANSITION

An Overview

"Compelled to yield to the power of time, women now cease to exist as the species, and henceforward live only for themselves. Their features are stamped with the impress of age, and their genital organs are sealed with the signet of sterility" (Hygiene Rules Relative to the Change of Life, 1850).

1.1 Stages of Menopausal Transition:

The transition of women from what the 19th century author of Hygiene Rules described as being a part of "the species", to becoming a separate sterile entity does not occur overnight. Menopausal transition is made up of a number of distinct stages, which usually commence during the mid to late 40s.

One of the problems often encountered in interpreting research findings relating to menopausal transition is the inconsistent use of the terms that describe the various stages of transition. In 1981 the World Health Organisation (WHO) attempted to rectify this situation by recommending

specific definitions that could be used to describe the pre-menopausal, peri-menopausal, menopausal and post-menopausal stages of transition. Despite this, definitions of transitional stages used in published research studies still vary.

1.1.1 Pre-Menopause:

The World Health Organisation (WHO), (1981) saw pre-menopause as an ambiguous term used to describe either the one to two year period prior to the cessation of menses, or the whole of the reproductive period prior to menstrual cessation. Apart from its definition as the whole of the reproductive period prior to menstrual cessation, pre-menopause has also been variously described in recent literature as encompassing:

- women who experienced their last menstruation in less than the previous 12 month period (Huerta, Mena, Malacara, & de Leon 1995a, 1995b),
- women who menstruated regularly in the previous three month period (McKinlay, Brambilla, & Posner,1992),
- women who did not self-report any symptoms associated with menopause (Shaver, Giblin, Lentz, & Lee, 1988; Shaver, Giblin, & Paulsen, 1992; Abraham, Llewellyn-Jones, & Pertz, 1994),

- women with low scores on the self-report Oestrogen Level Assessment Questionnaire and who also self-reported menstrual cycle irregularity (Baker, Simpson, & Dawson, 1997),
- women who experienced no changes in menstrual frequency in the previous 12 month period (Garamszegi, Dennerstein, Dudley, Guthrie, Ryan, & Burger, 1998).

1.1.2 Peri-menopause:

WHO (1981) recommended that the term peri-menopause be used as a global descriptor of the period immediately prior to, and at least one year after the menopause, characterised by physiological and clinical features of ovarian involution. However, research studies published during the 1990s have defined peri-menopause variously as:

- from three to 11 months amenorrhoea (no bleed) or increased menstrual irregularity (McKinlay, Brambilla, & Posner, 1992; Brambilla, McKinlay, & Johannes, 1994),
- a change in menstrual frequency or flow within the prior 12 months (Dennerstein, et al.,1993),
- a change in menstrual frequency/flow within the prior 12 months, that is also accompanied by menopausal symptoms (Hay, Bancroft, & Johnstone, 1994),

- a change in menstrual frequency in the previous 12 months, or three to 11 months amenorrhoea (Garamszegi, et al., 1998).

1.1.3 Menopause:

According to WHO (1981) menopause signifies the permanent cessation of menstruation, resulting from a loss of ovarian follicular activity. However, in most epidemiological literature menopause is now described as the last menstrual period, observed retrospectively as 12 consecutive months of amenorrhoea, without an obvious cause (McKinlay, et al., 1992; Dennerstein et al., 1993; Brambilla, et al., 1994,). The cessation of menstruation can also occur as a result of surgical intervention. Thus, the term 'without an obvious cause' can be seen to refer to the absence of prior surgical intervention.

To distinguish between surgical and spontaneous menopause, WHO (1981) recommended that the term 'surgical menopause' be applied only to women who had undergone bilateral ovariectomy with or without a hysterectomy. This definition recognised that normal ovarian function may continue after a simple hysterectomy (Merry, & Holeham, in Timiras, 1994). Here again, however, there are inconsistencies within the literature. For

example the Massachusetts Women's Health Study (McKinlay, et al., 1992) used the term 'surgical menopause' as inclusive of women who had undergone surgical removal of their uterus, but had not necessarily undergone bilateral ovariectomy.

1.1.4 Post-Menopause:

The definition of post-menopausal status recommended by the World Health Organisation (1981) was the period of life remaining after the menopause. Taking into account the WHO definition of menopause (the permanent cessation of menstruation due to loss of follicular activity) and peri-menopause (the period immediately prior to, and at least one year after the permanent cessation of menstruation), this definition of post-menopausal status related only to amenorrhoea.

However, other symptoms of menopausal transition can remain for several years after permanent cessation of menstruation. Eight years before the World Health Organisation (1981) defined post-menopausal status, a longitudinal study of women in Aberdeen, Scotland (Thompson, Hart, & Durno, 1973) looked at flushing experiences of women during menopausal transition. While 31% of participants did not experience any flushing during transition, Thompson, et al. reported the peak incidence of flushing as

occurring within the first 24 months after the completion of 12 months amenorrhoea. However, they also noted that, of the women who were still experiencing flushing after this period, 42% continued to flush for the next three to four years, with 50% still experiencing flushing from four to nine years later. Their findings have been supported by more recent research showing many women who achieve 12 consecutive months of amenorrhoea still experience menopausal symptoms linked with mood and flushing (Freedman, 1989; Swartzman, Edelberg, & Kemmann, 1990; Hay et al., 1994; Hunter, & Liao, 1995).

1.1.5 Transitional Definitions Used in this Study:

Research cited in Chapter 2 (A Review of Literature) has used the terminology of its various authors, when describing menopausal stages. The following terms were used within the present research study:

- **menopausal transition:** the total time from the commencement of menstrual irregularities and/or amenorrhoea to the time when all symptoms of menopause have ceased,

- **inception of peri-menopause:** at least three months amenorrhoea, or commencement of menstrual irregularity (ie menses that are more or less frequent than previous bleed patterns),

- **peri-menopause:** from three to 11 months amenorrhoea, or increased menstrual irregularity.

- **menopause**: the specific time-point at which twelve consecutive months of amenorrhoea has been achieved,

- **surgical menopause:** occurring in women who have undergone a bilateral ovariectomy,

- **post-menopause:** the point at which all symptoms associated with menopausal transition have ceased.

To distinguish between women who were undergoing menopausal transition without the use of hormone replacement therapy (HRT) and those who were using HRT;

- **natural transition** was used to designate women who were currently undergoing menopausal transition without the use of HRT,

- **HRT-assisted transition** was used to designate women who were currently using any form of hormone replacement treatment.

1.2 Age at Commencement of Menopausal Transition:

Determining the exact age at which women enter their menopausal transition is compounded by a number of factors. Retrospective sampling, by asking women to recall the date of their last regular menstrual cycle, can be biased by memory error, with women more inclined to remember their age at the time their periods became irregular, rather than the actual month when the irregularities commenced. There is also a tendency to retrospectively round up to the nearest five years, which can result in an artificially high incidence of the commencement of menopausal transition at the ages of 40, 45, and 50 (McKinlay, Jeffreys, & Thompson, 1972).

One of the earlier and comprehensive longitudinal cohort study of women undergoing natural menopausal transition in the Western world was the Massachusetts Women's Health Study (MWHS) (McKinlay, et al., 1992). This five-year study followed the menopausal transition of some 2,570 middle-aged women who lived in and around the environs of Massachusetts, USA. The study reported the median age, within their participant population, for commencement of menopausal transition as 47.5 years, with the median

age at menopause (defined retrospectively as 12 consecutive months of amenorrhea) occurring at 51.3 years.

While the MWHS looked at North American women, other studies have reported a similarity at age of menopause between women of differing ethnic groups (see Gray, in Beard, 1976). Discussing factors that influence age at menopause, Timiras (1994) discounted ethnicity *per se*, pointing to the similarity between median age at menopause of Caucasian and Negro women living in North America (median age cited as 50 and 49.3 years of age respectively) and South Africa (50.4 and 49.7 years respectively). Similarly, little difference was seen between the mean age (comparative median not available) at menopause of women of British origin (49.5 years), women of Japanese origin (49.3 years), and educated women of Central Javanese origin (50.2 years).

What is of interest in defining age at menopause is not ethnicity, but other factors that affect women regardless of their ethnic backgrounds. For example, research has shown issues as varied as smoking and marital status can have an effect on the age of inception of menopausal transition. One of the most pertinent findings of the MWHS (McKinley et al, 1992) was the strong relationship between current cigarette smoking and earlier age of

commencement of menopausal transition, with a median shift of around 1.5 years.

An earlier study (McKinlay et al, 1971) that investigated the age at which women had their final menses investigated both marital status and socio-economic status (SES). From a representative sample of some 736 mid-aged women, McKinlay, et al. (1971) noted that women who were currently married at the time of the study ceased menstruation later than those women who were widowed, divorced, separated, or had never married. Interestingly, when considering only the currently married participants, McKinlay et al. (1971) found a relationship between later cessation of menses and higher socio-economic status.

Other studies have also pointed to a relationship between socio-economic status (rather than ethnicity), and the age at onset of transition, with consistently poor nutrition appearing the most effective predictor of early menopausal transition. A study of Melanesian women living in rural areas of New Guinea (Scragg, 1973), found that while the median age for onset of transition in well-nourished Melanesian women was 47.3 years, the onset age of malnourished women within the same population dropped to 43.6 years. This link between consistently poor nutrition and subsequent lower body weight and stature has also been supported by Sherman, Wallace

and Treloar (1979), who argued that age at transitional onset was directly related to body fat percentages in early adulthood.

Thus, the closeness in age at onset of transition between well-nourished populations who are geographically and ethnically separated (Scragg, 1973, McKinlay et al, 1992) would suggest that 47 $\pm$0.5 years could be considered as the median age for transitional commencement in the majority of Australian women, regardless of their ethnic background.

1.3 Hormonal Changes during Menopausal Transition:

Hormones are often described as the chemical messengers of the central nervous system (Raven, & Johnson, 1992). Rather than use electrical signals that must be transmitted via each individual neural synapse, hormones can be spread to tissues throughout the body via the endocrine glands and the blood system. While exocrine glands directly secrete substances such as sweat, milk and digestive enzymes, the ductless endocrine glands produce large amounts of hormones. These hormones are produced in response to neurohormonal signals initiated by the central nervous system. Their distribution relies upon a molecular signal and a highly specific protein receptor designed only to accept that particular molecular signal.

The principal endocrinal glands within men and women are the posterior and anterior pituitary gland, the thyroid gland, the parathyroid glands, the adrenal medulla and adrenal cortex, the islets of Langerhans, the ovaries, the testes, and the pineal gland.

1.3.1 Endocrinal Hormone Activity during the Normal Menstrual Cycle

While many lower animals exhibit reproductive functions that undergo cyclical changes in preparation for fertilisation and pregnancy, only primates and humans exhibit a reproductive, or menstrual cycle, with ovulation occurring during the mid-point of the cycle (Hogden, Goodman, O'Connor, & Johnson, 1977). In most human females, this endocrinal menstrual cycle takes 28 days to complete.

The full nature of what drives this cyclical rhythm is as yet unknown. However, research in the early 1980s in rats suggested that the neural regulation of oestrogen-induced gondatrophins was mediated by the supra-chiasmic nucleus (SCN), via the retino-hypothalamic tract (Kawakami, Arita, & Yoshida, 1980). Substantial information about this tract in sub-mammalian vertebrae first became evident in the 1940s, but it was not until the early 1970s that definitive evidence of a similar tract in mammals was reported. Using autoradiography to follow the path of a labelled amino acid (triated leucine) Moore and Lenn (1971) were able to map a direct projection

from the retina of albino rats to the supra-chiasmic nucleus of the medial hypothalamus. Subsequent research (Voordouw, et al.,1992) looked at the possible role played by melatonin in the ovulation cycles of women. They concluded that during the evolutionary process of mammalian reproduction, the neuroendocrine mechanisms by which animals regulate fertility in a seasonal fashion (see Chapter 5.3), remains essentially intact in women and can be stimulated by exogenous melatonin/progestin combinations.

The hormonal activity that regulates the monthly menstrual cycle is controlled by an interconnected neuroendocrine feedback loop, known as the hypothalamic-pituitary-ovarian axis (Jensvold, in Stewart, & Stotland, 1993). When the first day of menstruation occurs, the hypothalamus expels gonadotrophin-releasing hormone (GnRH) into the bloodstream supplying the pituitary gland. The action of GnRH on the pituitary gland initiates the secretion of follicle stimulating hormone (FSH). This increase in FSH results in the growth within the ovaries of some 10 to 20 small egg sacs, or follicles. During their growth, the follicles stimulate the production of the hormone oestrogen which, in turn, stimulates the growth of uterine mucosa, a soft lining made up of a number of narrow tubes known as the endometrial glands. These glands are set in layers of endometrial stromal cells that, when stimulated by oestrogen, proliferate. As the follicles continue to grow, oestrogen levels continue to rise. At around thirteen days from the onset of

menstruation, it has been estimated that oestrogen has risen to six times its level at menstrual onset. It is this increase in oestrogen that produces the feedback loop in the hypothalamus, effecting a change in the GnRH being supplied to the pituitary gland.

The pituitary gland also houses specialised cells that produce lutenising hormone (LH). Around the fourteenth day from the onset of menstruation, a surge of LH enters the blood stream and makes its way to the ovaries. While many of the follicles will have degenerated, several will continue to grow. At this stage they resemble small, but tightly stretched balloons. The largest of the follicles will, by now, have reached the surface of the ovary, where the sudden onset of lutenising hormone induces bursting of the follicle. The egg contained within the follicle is expelled, and enters oviduct, from where it slowly moves down into the oviduct tube cavity, in preparation for fertilisation.

The empty follicle collapses, and turns yellow. It is this action that gives rise to the name lutenising hormone, from the Latin *luteus*, or yellow. The burst follicle, together with the remaining unburst follicles, continue to secrete oestrogen, but now also start to produce the hormone, progesterone. The purpose of progesterone, as its name suggests, is to prepare the uterus for possible pregnancy (*progestos*). Progesterone thickens the lining of the

uterus and elevates body temperature, but more importantly, it induces a nutritious secretion from the endometrial glands to feed the potentially fertilised egg during its implantation into the lining of the uterus.

If fertilisation does not occur, the remaining follicles and the burst follicle degenerate and die. This, in turn, results in a decrease in the levels of oestrogen and progesterone in the blood. As a result of this decrease, GnRH is again released at full levels into the blood stream allowing the pituitary gland to increase production of FSH. Without increased production of oestrogen and progesterone, the thick lining of the uterus shrinks, breaking the thin blood vessels within it. The breaking of these blood vessels causes a build up of bleeding within the uterine layers. After several hours the bleeding reaches a point at which the uterus starts to contract. These contractions expel the uterine lining, together with the surplus blood, into the cervix and, from the cervix into the vagina. Menstruation is now said to occur and the menstrual cycle is completed.

1.3.2 Endocrinal Hormone Activity during Menopausal Transition:

Changes in endocrinal hormone activity during menopausal transition were initially thought to occur as a result of the cells surrounding the ovarian follicles becoming less receptive to the pituitary hormones in the blood stream. Llewellyn-Jones and Abraham (1988), proposed that in an effort to

counteract this poor response follicle stimulating hormone (FSH) levels were increased, thus altering the proportion of FSH to lutenising hormone (LH) during the monthly cycle. This, they suggested, led to an alteration in the balance between FSH, secreted to enhance the growth of the follicles, and LH, secreted to ensure the bursting of the larger follicle. Over time follicle production decreased, with a resultant decrease in oestrogen and progesterone production, as the follicles became less and less receptive to the pituitary hormones. Eventually the uterus no longer received the stimulus to expel the uterine lining and menstruation ceased to occur.

More recently, however, reproductive endocrinal studies have pointed to the selective (or monotrophic) rise in the level of FSH, unaccompanied by a commensurate rise in LH, as being the most consistent indicator of reproductive aging (Klein, et al., 1996). In comparing the menstrual cycle of a group of young women (mean age 23.5 years) and older women (mean age 43.6 years) Klein, et al. noted that the older women developed their dominant follicle much earlier in their cycle. In these women the highest FSH concentration (11.4±0.5 IU/L vs. 8.0±0.4 IU/L) occurred on cycle day 3.3 (±0.6) as opposed to cycle day 8.4 (±0.8) in the younger women. This earlier rise in monotrophic FSH levels was also accompanied by a significant decrease in inhibin-B (INH-B) production, although levels of inhibin-A (INH-A) were similar in both groups.

During the normal menstrual cycle, follicular inhibin, secreted by the ovarian follicles, selectively inhibited FSH secretions. While INH-A appeared to be the product of the larger of the follicles, INH-B was thought to result from the activity and/or size of the initial follicle group (Klein, et al., 1996). The monotrophic rise in FSH levels is currently believed to be the best predictor of onset of menopausal transition (Vakkuri, Kivela, Leppaluoto, Valtonen, & Kauppila, 1996). Thus, decreased levels of INH-B, suggestive of a diminishing follicle pool, may be a significant regulator of the sudden increase in FSH levels of women entering their menopausal transition (Klein, et al., 1996).

Recent Australian research also supported the gradual decline in follicle numbers being linked to a consequential fall in INH-B and a resultant increase in FSH levels. Burger, et al. (1998) suggested that, even during irregular transitional cycles, dominant follicles were still produced and thus oestrogen and INH-A secretions remained at somewhat stable levels during the follicular stage of the menstrual cycle. However, as age increased, follicle numbers continued to decline, leading to a commensurate drop in INH-B levels, and a resultant increase in follicle stimulating hormone. This increase in FSH allowed the dominant follicle within the irregular transitional cycle to maintain the secretion of oestrogen and INH-A, thus maintaining ovulatory

function during the early years of menopausal transition (Burger, et al., 1998). Eventually, however, initial follicle numbers declined to such a level that they become insufficient to maintain INH-B levels, despite the increase in FSH levels. At this time, oestrogen and INH-A levels fell, and ovarian function ceased. Burger, et al. (1998) concluded that falling follicle numbers and the resultant drop in production of INH-B was the hormonal trigger for increasing levels of FSH, which sustained production of oestrogen and INH-A well into menopausal transition.

CHAPTER 2

SYMPTOMS ENCOUNTERED DURING MENOPAUSAL TRANSITION

A Review of Literature

> ***"And here it will not be amiss to touch upon the Disorders that most Women labour under, when being between forty and fifty years of Age, their Courses begin first to dodge and at last to leave them; for then they are frequently troubled with a Severe Pain in the Head and Back, and about the Loins; oftimes also with Cholick Pains, Gripes, and Looseness, at other Times with Vapours to a Violent Degree; likewise feverish Heats, wandering Rheumatick Pains and general Uneasiness"*** (Un-named English Physician, circa 1799, in Saltman, 1994).

2.1 Common Menopausal Symptoms:

This 18th century description of menopausal symptoms, while archaic in its terminology, still provides a fairly accurate description of some of the more common symptoms of menopausal transition. In the Massachusetts Women's Health Study (McKinlay, et al., 1992) the following 22 common health signs or symptoms that related to menopausal transition were identified:

- Hot flushes/flashes, cold sweats, vertigo (dizzy spells), feeling blue or depressed, headaches, insomnia (trouble sleeping), palpitations (rapid heart beat), lack of energy, diarrhoea and/or constipation, persistent cough, backaches, upset stomach, aches/stiffness in joints, shortness of breath, sore throat, loss of appetite, menstrual problems, fluid retention, difficulty in concentration, nervous tension, urinary tract or bladder infections, and 'pins and needles' in either hands or feet.

Over the duration of the study, McKinlay, et al. (1992) found the three most frequently cited symptoms were hot flushes/flashes, cold sweats and insomnia. Of women who reported hot flushes/ flashes, almost 50 percent also reported cold sweats. As problems with sleep were more than twice as likely to be reported by the women who also reported hot flushes, it was suggested sleep disturbances could be due to nocturnal flushing episodes.

Another large-scale study that examined menopausal symptomatology arose from the Rancho Bernado Study. From 1972 to 1974, some 82% of all Caucasian women who lived in the Southern Californian community of Rancho Bernado took part in a study of risk factors for heart disease. In 1989 589 women from the initial Rancho Bernardo study were invited to take part in a retrospective study of menopausal symptomatology (von Muhlen, Kritz-Silverstein, & Barrett-

Connor, 1995). Their mean age at menopause (defined as 12 months cessation of menses), was reported as 48.8 ±5 years. Twenty-seven percent of participants reported their current use of hormone replacement therapy, while 42% were past users. Average duration of HRT was 8 ±8.3 years.

In addition to questions on their use of HRT, women who participated in the Rancho Bernado study (von Muhlen, et al., 1995) were also asked to complete a retrospective checklist. Apart from common menopausal symptoms, the checklist also included questions relating to mood and lifestyle issues, using the criteria "at the time of menopause, how did you feel as compared to before?" The most frequently listed transitional symptoms were hot flushes (74%) weight gain (45%), night sweats (35%), tiredness (32%), and poor sleep (28%). However, one fourth of participants also reported irritability, and one fifth reported feelings of depression. Using principal component factor analysis, the largest variance(21%), was accounted for by what von Muhlen, et al. termed 'psychological' symptoms (irritable, depressed, weepy, unable to sleep well). While vasomotor symptoms accounted for the next highest variance (14%), night sweats, rather than hot flushes or visible flushes accounted for the largest factor loading (0.75).

In the early 1990's, the Key Centre for Women's Health in Society (Melbourne, Australia) was also seeking to describe Australian women's

experiences during menopausal transition. Using similar criteria to the American MWHS (McKinlay et al., 1992) the Melbourne study recruited some 2,000 Australian-born women aged between 45 to 55 years to take part in what was termed the Melbourne Women's Midlife Health Project (MWMHP). In their initial cross-sectional study design (Dennerstein, et al., 1993), participants were asked whether, in the previous two weeks, they had experienced any of the 22 health related signs and symptoms used in the Massachusetts Women's Health Study. Using factor analysis, results showed the major variance loading (13.9%) was accounted for by nervous tension, feeling sad or downhearted, difficulty in concentration, lack of energy and trouble sleeping. The next major variance was accounted for by the vasomotor symptoms of hot flushes and cold sweats. Night sweats were not included in either the MWHS or MWMHP symptom lists.

The Massachusetts Women's Health Study did not report variance levels. However, results from both the Rancho Bernado study and the Melbourne-based Women's Midlife Health Project, reported the most commonly cited menopausal symptom cluster was that associated with sleep disturbance, feelings of tiredness, irritability, tearfulness, nervous tension and depression.

2.2 Symptom Definitions Used in this Study:

While von Muhlen et al. (1995) used the term 'psychological' to refer to the cluster of symptoms covered by sleep disturbance, irritability,

depression and tearfulness, other researchers (Shaver, et al.,1991; Shaver, & Paulsen, 1994) have used the term 'somatic' as the descriptor of symptom clusters that included vasomotor symptoms (flushes and sweats), musculoskeletal symptoms (muscle, joint and back pain), gastrointestinal symptoms (stomach pain, constipation and diarrhoea), autonomic nervous symptoms (dizziness and palpitations) and fatigue or tiredness. In their factor analysis of results from the initial cross-sectional survey carried out by the Melbourne Women's Midlife Health Project, Dennerstein, et al. (1993) grouped the menopausal symptoms of nervous tension, sadness or downheartedness, difficulty in concentration, lack of energy and problems sleeping under the umbrella term 'dysphoria'. Symptoms relating to hot flushes and cold sweats were designated as 'vasomotor' symptoms.

Defining the cluster of menopausal symptoms that include flushes and/or sweats, muscle, joint and/or back pain, stomach pain, constipation and/or diarrhoea, dizziness, palpitations, fatigue and/or tiredness as 'somatic' suggest they are purely physiological in origin. Equally, menopausal symptoms which cause sleep disturbance, irrational mood swings, sudden onset of tears, and feelings of worthlessness, may be seen by many transitional women as the bearer (Greek: *phorus)* of something bad (Greek: *dys*). However, this thesis will use the term 'psychogenic' (after Utian, in Beard, 1976), when describing the cluster of transitional

symptoms encompassing trouble sleeping, lack of energy, feelings of sadness/downheartedness, nervous tension and difficulty in concentration.

Autonomic nervous system imbalances are thought to be responsible for such menopausal symptoms as hot flashes/flushes, palpitations, perspiration/sweats and angina pectoris (Merry, & Holeham, in Timiras, 1994). These symptoms are often globally described as 'vasomotor' symptoms. More specifically, menopausal hot flushes appear to occur as a result of a disorder within the medial preoptic area of the hypothalamus; the area responsible for initiating the body's thermoregulation (Woodward, & Freedman, 1994). To distinguish flushes and/or sweats that occur only during the night from daytime vasomotor symptoms experienced during menopausal transition, this thesis will use the terms nocturnal thermoregulatory symptoms, or nocturnal (night) flushes and/or sweats.

2.3 Psychogenic Symptoms of Menopausal Transition:

It has been suggested that the best predictor of both well-being and depression in mid-aged women is tiredness (Cawood, & Bancroft, 1996). Poor sleep quality or inadequate amounts of sleep within a transitional population, have also been linked to chronic fatigue, lack of motivation, lack of concentration, feelings of tension, irritability and physical unwellness (Shaver, & Paulsen, 1993).

Reviewing data obtained from the 1989 USA National Ambulatory Medical Survey, Shaver and Paulsen (1993) noted that during the whole of that year women aged from 45 to 64 years accounted for some 13% of all visits made to office-based North American medical practitioners. From a list of the top 60 reasons given by these women for their medical visits, symptoms such as tiredness, exhaustion, fatigue, depression, anxiety, nervousness, muscular aches and pains and dizziness all featured in the top 36 reasons. Some years previously, a study of approximately 7,000 San Francisco Bay residents (Welstein, Dement, Redington, Guilleminault, & Mitler, 1983) had reported that 31% of participants (aged from six to 103 years) reported problems with sleep. Of this 31%, 62% were women aged between 45 to 54 years. Using this latter study as a primary reference, Shaver and Paulsen (1993) sought to investigate the relationship between sleep quality, psychological distress and what they referred to as 'somatic' symptoms (see Section 2.2) in a mid-aged female population. Over a period of six years, 135 women between 37 and 59 years of age took part in a two-stage, two group study. In addition to questionnaire-based research, the study included spending two nights in a sleep laboratory for objective assessment of sleep quality. Of the overall 135 participants, 82 were classified as peri- or post-menopausal, with 59% self-reporting poor sleep. Results from the polysomnographic (sleep laboratory) component of the study indicated that both peri- and post-menopausal women who reported poor sleep took significantly longer to

fall asleep, with longer sleep latencies to sleep stages 1 and 2, and to slow wave sleep (SWS) than their counterparts who self-reported good sleep.

Looking at the relationship between sleep quality and psychological distress, Shaver and Paulsen (1993) found a significant main effect for all but one of the 12 criteria on the SCL-90 scale of psychological distress. Self-reporting poor sleepers demonstrated higher levels of psychological distress than participants who self-reported good sleep. Similarly, in all but one of the somatic symptom clusters (gastrointestinal problems) poor sleepers reported significantly higher frequencies of somatic symptoms than their good sleeping counterparts.

Transitional women in the Shaver and Paulsen (1993) study were required to spend two nights in the unfamiliar surroundings of a sleep laboratory. However, Baker, Simpson and Dawson (1996) used wrist actigraphy to assess the relationship between quality of sleep and mood changes in an aged-matched pre- and peri-menopausal population. Although a relatively new device for monitoring sleep quality in a home environment, use of wrist actigraphs had shown a high degree of concordance with polysomnography (PSG) for differentiating sleep from wake (Drennan, Kripke, Klemfuss, & Moore, 1991; Sadeh, Lavie, Scher, Tirosh, & Epstein, 1991; Cole, Kripke, Gruen, Mullaney, & Gillen, 1992; Sadeh, Sharkey, & Carskadon, 1994). Subsequent development of miniaturised monitoring devices led to physiological data monitoring

devices (PDMDs) that could concurrently monitor diurnal or nocturnal activity, body temperatures, heart rate, etc. Thus the term "wrist actigraphy" is somewhat redundant. However, in this context is was normal usage to describe monitoring of nocturnal sleep activity as wrist actigraphy. Taking into account the problems with adaptation to a sleep laboratory environment, it was argued that wrist actigraphy gave a more ecologically valid picture of typical sleep and wakefulness than PSG (Cole, et al., 1992).

Baker, et al. (1996) reported a significant difference in actigraphically monitored sleep quality between pre- and peri-menopausal women. While there was no significant difference between the actual time spent in bed, participants who were classified as peri-menopausal were shown to have significantly greater sleep disruption, with more arousal time across the whole sleep period than their age-matched pre-menopausal counterparts. Baker, et al. (1996) also noted significant differences between pre- and peri-menopausal participants on measures that related to sleep quality and mood. Within the peri-menopausal group there were several significant correlations between sleep variables and sub-scale Profile of Mood Scale (POMS) scores for fatigue, depression, tension and confusion. However, there were no significant correlations between any POMS sub-scale scores and sleep variables within the participants classified as pre-menopausal. These results led Baker et al. (1996) to suggest a relationship between quality of sleep and mood,

where levels of sleep disruption could be seen as having a role in the mediation of mood and anxiety levels during menopausal transition.

Further evidence of a link between quality of sleep and other psychogenic symptoms has come as a result of a community-based study of 141 British women (Cawood, & Bancroft, 1996). This study had sought to investigate the relationship between ovarian and adrenal hormones and both sexuality and well-being in women aged between 40 to 60 years. Their initial predictor variables were age, body mass index, cigarette smoking behaviour, hormonal levels of oestradiol and oestrone, socio-economic status, hormonal levels of dehydroepiandrosterone, menopausal status, and prevalence of diurnal and nocturnal flushes and/or sweats. Psychological well-being was assessed using the Multiple Affect Adjective Check List (MAACL). The MAACL provided for self-rating of depression, anxiety, hostility, positive affect and sensation seeking, in addition to two composite scores of dysphoria and positive affect plus sensation seeking. Using multiple regression, Cawood and Bancroft (1996) took positive affect (and sensation seeking), hostility, and depression as the dependent variables of the construct well-being. They noted that several participants had commented on the lack of adjectives within the MAACL for rating tiredness. The only measure of tiredness available to the study came from a question on a 29-item menopausal symptom questionnaire (MSQ), then in use at the Edinburgh Menopause Clinic and cited as derived from Greene, 1976. The MSQ had been administered to participants as part of

an initial interview, and in view of the comments made regarding tiredness, participant rating for this item was added to the other predictor variables. The results of this study showed the only significant predictor of feelings of both well-being and depression to be tiredness. Tiredness was the main negative predictor of well-being and the only significant positive predictor of depression. In discussing their results, Cawood and Bancroft (1996) noted that future treatment studies should pay more attention to systematically assessing the effect of tiredness on feelings of psychological well-being within a menopausal population.

While not looking at a specifically mid-aged female population, Libbus, Baker, Osgood, Phillips, & Valentine (1995), also reported a relationship between feelings of fatigue and psychological well-being in women. In a cross-sectional study of 155 North American women (aged between 21 to 60 years) who identified themselves as being persistently fatigued, but otherwise well, Libbus, et al. noted a significant relationship between fatigue and feelings of depression. Statistical analysis of scores obtained from the Piper Fatigue Scale (PFS) and the Beck Depression Index (BDI), showed that women who experienced greater fatigue (as demonstrated by higher scores on the PFS), also had higher scores on the BDI. As the higher BDI scores were at the lower end of the range for mild to moderate depression, Libbus, et al. suggested that persistent fatigue could be an antecedent to mild-moderate depression. Equally, they noted

that even mild mood disturbances could have a considerable effect on perceptions of psychological well-being.

In their 1997 study, Dennerstein, Dudley, and Burger, assessed psychological well-being within a menopausal population using a scale designed to measure current levels of general happiness (Affectometer 2). This scale provided scores for psychological well-being, positive affect, and negative affect, where overall well-being was assessed as the difference between the positive and negative affect scales. The study noted that positive affect decreased across the transitional spectrum, but was only significantly lower ($p < .05$) in women who had achieved 12 to 24 consecutive months amenorrhoea. Negative affect increased across the transitional spectrum, being significantly higher in all but those women who had achieved more than 24 consecutive months amenorrhoea. The authors concluded that there was an overall trend for well-being to decrease with increasing transitional status, with lowest levels occurring in women in the 12 to 24 month amenorrhoea category. However, as feelings of psychological well-being began to improve again after 24 consecutive months amenorrhoea, this decline in feelings of psychological well-being during menopausal transition could, in the authors' opinion, be viewed as being of a transitory nature.

2.4 Thermoregulatory Symptoms of Menopausal Transition:

Within a transitional population, poor sleep quality, with resultant fatigue, had been shown to be associated with higher levels of other psychogenic menopausal symptoms known to affect feelings of psychological well-being (Shaver, & Pauslen, 1993, Baker, et al., 1996, Cawood, & Bancroft, 1996, Libbus et al., 1995). McKinlay et al. (1992) suggested a main contributor to this poor sleep quality could be frequent awakenings caused by nocturnal flushes/sweats. (For a more detailed account of the thermoregulatory physiology of menopausal hot flushes/sweat see Chapter 5.3.3). Briefly, hot flushes have been generically described as a sudden sensation of heat radiating from the skin over the face, neck and chest area. This sudden heat is occasionally followed by a chill, but is usually associated with sweating or perspiration. The flushing sensation may be accompanied by a reddening of the skin (visible flushes), feelings of anxiety, tingling and/or feelings of tightness around the head. For a more detailed description of the pathophysiology of hot flushes/flashes, the reader is referred to Frishman (1995).

In the three large studies of transitional women (McKinlay, et al., 1992, Dennerstein, et al., 1993, Von Muhlen, et al., 1995) the cluster group of diurnal and/or nocturnal flushes and/or sweats had been reported as one of the most frequently occurring symptoms. Results from the initial cross sectional study of the Melbourne Women's Midlife Health Project (MWMHP) (Dennerstein, et al., 1993) showed that 31.5% of peri-

menopausal and 39.4% of post-menopausal women had reported an occurrence of such flushes in the previous two weeks, as compared to only 9.8% of their pre-menopausal counterparts.

In a follow-up study by Guthrie, Dennerstein, Hopper, and Burger (1996), women who were classified as pre-menopausal at the time of the initial MWMHP cross-sectional study were invited to take part in a further study. This study was designed to determine the frequency of flushing, and its relationship to such variables as menstrual status, serum levels of estradiol (E2), inhibin and FSH, body mass index (BMI), lifestyle factors (eg. caffeine and alcohol intake, cigarette smoking behaviour, physical activity) and previous menstrual history. Blood samples, reports of flushing frequency, lifestyle and dietary information were obtained from 438 women, whose ages ranged from 48 to 59 years. The results showed an increased incidence of flushing as transition progressed. While 13% of participants who were still classified as pre-menopausal reported flushes, this increased to 37% in women who had experienced more than three, but less than 11 months amenorrhoea (termed peri-menopausal in this study). Of women who had achieved more than 12 consecutive months amenorrhoea (termed post-menopausal), almost two-thirds (62%) reported at least one flushing episode per week, with 25% reporting multiple flushing episodes. While analysis of results showed evidence of a relationship between increasing FSH levels and decreasing E2 levels in flushing as opposed to non-flushing in women defined as peri-

menopausal, neither hormonal status nor lifestyle factors identified why some, but not all, participants defined as post-menopausal experienced flushing episodes.

Unlike the above study by Guthrie et al. (1996) that looked only at diurnal flushing episodes, the Rancho Bernardo study (von Muhlen, et al., 1995) did seek to distinguish between flushes that occurred during the day, and flushes/sweats that occurred during the night. Of the 74% of participants who recalled any flushing experiences, almost half reported nocturnal flushing episodes. Recalled age at incidence of flushes varied only with nocturnal episodes, with significantly more of the younger women reporting night sweats. Although this study also reported a significant relationship between increased incidence of thermoregulatory symptoms and an increased incidence of psychogenic symptoms, no breakdown was given between such incidence and either diurnal or nocturnal flushing experiences.

When looking specifically at the relationship between sleep parameters and nocturnal thermoregulatory symptoms, research is still somewhat limited. Using polysomnography (PSG), Shaver, et al. (1988) reported that both peri- and post-menopausal women who experienced nocturnal flushes and/or sweats had significantly longer rapid eye movement (REM) latencies and lower sleep efficiencies than their non-symptomatic counterparts. After controlling for age and depressive

symptoms (indicated by scores on SCL-90), flushing and non-flushing women were seen to differ significantly on measures of sleep efficiency, while REM latency continued to show a trend toward a group difference (Shaver, et al., 1988). Woodward and Freedman (1994) also compared the sleep architecture of women (n=12) who had achieved at least 12 consecutive months amenorrhoea and were still experiencing diurnal and nocturnal flushing episodes with asymptomatic women (n=7) who had never experienced diurnal or nocturnal flushing episodes. They found that the symptomatic group slept less efficiently than the non-flushing group ($p < .05$), woke more often ($p < .01$) and had significantly more sleep stage changes ($p < .05$). While not commenting on REM latencies, they did note that the women who reported nocturnal flushes also experienced a shorter first REM period ($p < .01$). While there was no significant difference between the two groups during the first period of non-rapid eye movement sleep (NREM1), there was a significant reduction in NREM sleep in period that followed the shorter first REM stage. During this second NREM period, symptomatic women had significantly more stage 4 slow wave sleep than asymptomatic women. In fact, they had significantly more stage 4 sleep throughout the entire sleep period ($p < .01$) than asymptomatic counterparts. This would suggest that the symptomatic group were more sleep deprived, with more pressure for slow wave sleep.

While the above research points to a change in the sleep architecture of transitional women who experience nocturnal flushing,

other research has suggested that the flushes themselves are not the primary cause of such mid-sleep awakenings. In a sleep laboratory-based study of transitional women selected on the basis of self-reported severe nocturnal flushing episodes, it was shown that in 45 out of 47 objectively measured hot flushes, participants woke from sleep (Erlick, Takaryn, & Meldrum, 1981). However, in each of the 45 mid-sleep awakenings, waking fractionally preceded any increase in skin temperature. This may suggest that the discomfort caused by increased peripheral body temperature is not necessarily the primary cause of mid-sleep awakening in women who suffer from nocturnal flushing episodes. Research in this area is still somewhat limited. However, some other mechanism, or common central phenomenon, which precedes the flushing episode (as suggested by Gonen, Sharf, and Lavie, 1984) may be responsible for mid-sleep awakenings.

2.5 Psychosocial Adjustment and Menopausal Transition:

There is little doubt that flushing experiences are an extremely common feature of menopausal transition, but they are not seen as problematic for all women who experience them. When questioned about the debilitating effect of flushing episodes 26% of peri-menopausal women and 59% of post-menopausal women reported that they were "bothered" by their flushing episodes (Guthrie, et al., 1996). In this context, depressed mood and feelings of anxiety and low self-esteem have been reported as the main discriminators between transitional women who

regarded flushing as problematic and those who, while experiencing similar flushing, do not regard their flushing experiences as problematic (Hunter, & Liao, 1995).

Although there is little doubt that menopause is a major life transition for women, it is not viewed as a major life crisis by all women. In attempting to establish a common thread between psychological problems and symptomatic effects of menopausal transition, some researchers have pointed toward differing environmental and social issues within the lives of these women. It has been argued that differing psychosocial factors play a major role in explaining why some people are able to deal successfully with such life transitions while, for others, such transitions become major life crises (Moos, & Schaefer, 1986).

In a historical overview of psychosocial issues encountered by women during their menopausal transitional, Sherwin (in Stewart, & Stotland, 1993) discussed early attempts to apply a psychosocial framework to the aetiology of menopause. Not surprisingly, the first link between transitional symptoms and psychosocial issues occurred within the psychoanalytic framework. Freudian theorists argued that the loss of child bearing ability, viewed then as central to a woman's life, could be seen to lead, during menopausal transition, to a loss of life's meaning. Within this early psychoanalytical framework, menopause was seen as a "symbolic castration" (Benedek, 1950, cited in Sherwin, 1993: 238) where

menopausal women were deprived of any compensatory means to dispel their anger and frustration at not being born male.

In the late 1960s and early 1970s, socio-cultural theories came into prominence. According to the socio-cultural model, the major determinants for psychological disturbance during menopause were founded within the woman's societal role change and society's attitude towards aging. Western societies were seen to be primarily capitalistic and youth-driven. The negative connotation that accompanied the stereotypical view of aging women did not, according to this model, provide a supportive environment for a successful menopausal transition (Sherwin, 1993),

Another major model put forward during the mid-1970s and early 1980s to account for the psychosocial health of transitional women was the post-parental phase, or "empty nest syndrome". For many women, the onset of menopausal transition coincidentally occurred at or around the time their children had left, or were about to leave the family home. However, psychological adjustment within this post-parental phase appeared more related to availability of interests outside the home than to the actual loss of child-bearing ability or the departure of children from the family home (Powell, 1977). Women who had pursued a career, or who were actively involved in community work, or had other interests outside the home, were seen to have significantly better mental health during

their transitional years than women whose role had been primarily restricted to that of mother and home-maker (Powell, 1977).

In the late 1980s, other 'transitional phenomena' (Sherwin, 1993) occurring at the same time as menopausal transition were thought to have had an impact on women's psychosocial health and the way in which they dealt with the symptoms of transition. Within the general scope of other 'transitional phenomena' were death of one or both parents, incapacity of one or both parents and subsequent need to provide nursing care, onset of personal or spousal major illness or disability, and/or uncertainty of continuing employment status for either their self and/or their partner.

Noting that research studies frequently ask women to list their menopausal symptoms but rarely examined issues regarding the effects of such symptoms on quality of life, Roberts, Chambers, Blake and Webber (1992) sought to establish the impact of HRT on the psychosocial adjustment of women in mid to late transition. During an 18-month intervention period 72 participating women received either (i) calcium supplements (not expected to have any effect on psychosocial health) and counselling, (ii) continuous HRT (Premarin and Provera), calcium supplements and counselling, or (iii) cyclic HRT regimes (separate combinations of Premarin and Provera) and counselling. Initially, results from a measure of psychosocial adjustment (Psychological Adjustment to Illness Scale) showed some 14% of the study population as having only

poor psychosocial adjustment to menopausal transition. However, when re-tested after the intervention, the results showed an 18% improvement in overall psychosocial adjustment, but no significant difference between the psychosocial adjustment levels of the calcium alone or the calcium plus HRT groups. As calcium alone could not account for improved psychosocial health within this placebo group, the authors concluded that the availability of counselling services, the ability to discuss menopausal-related concerns, and the greater access to reliable written material regarding transition had accounted for the improvement in psychosocial health, rather than any HRT regime.

When examining the relationship between premenstrual complaints and peri-menopausal experiences, Morse, Dudley, Guthrie and Dennerstein (1998) also concluded that HRT regimes alone provided insufficient treatment for those women who appeared most vulnerable to problematic symptom reporting during menopausal transition. They suggested that for these women, menopausal-related complaints were underpinned by psychosocial sources, where biosocial factors interacted with the women's psychological make-up to produce a complex set of health problems that seemed related to the menstrual cycle and operated as triggers for help-seeking behaviours.

Feelings of on-going sexual desirability have also been seen to affect some women's psychological health during menopausal transition,

with a decline in sexual interest significantly associated with decreased feelings of well-being, and higher menopausal vasomotor and skeletal symptom severity (Dennerstein, Smith, Morse, & Burger, 1994). Within the individual domains of psychosocial adjustment reported in the Roberts, et al. (1992) study, the three most poorly adjusted domains were those of health care orientation, followed by feelings of psychological distress and altered sexual relationships. Equally suggestive of a link between sexuality, menopausal symptoms and psychosocial health are findings from a study designed, in part, to investigate the relationship between psychogenic symptoms and attitudes towards sexual roles, lifestyle and family functions (Huerta, Mena, Malacara, & de Leon, 1995a). Transitional women's perceptions and attitudes towards their role, in terms of both physical attractiveness and sexual activity, were shown to be main regressors of many psychogenic symptoms. However, this sexual perception was also shown to be significantly associated with such psychosocial issues as the prior role adopted by both the male and female within the family structure in terms of the "traditional" housekeeper roles, and the post-parental lifestyle of the participants (Huerta, et al., 1995a).

Whether psychosocial factors result from a 'symbolic castration', a youth-driven society, a suddenly 'empty nest', a coming to terms with parental illness or death, uncertainty of continued employment, concerns of on-going sexuality, or a changing body image is a matter of speculation. For women, some or all of these potentially stressful events

certainly do occur at the same time as their menopausal transition, and may have an effect on their psychological health.

2.6 Hormone Replacement Therapy (HRT) and Menopausal Symptoms:

Over the past several decades hundred of studies have looked at issues relating to the use of HRT during and after menopausal transition. Many of these studies have been biomedically-based, and have concentrated on safety of use of a variety of oestrogen-based substances. Others have investigated the efficacy of HRT on symptoms associated with menopausal transition. To introduce even a fraction of this literature is beyond the scope of this thesis. However, of interest to this research study is the on-going disparity of research results in terms of the benefits or otherwise of HRT in relation to menopausal symptoms involved in mood changes and sleep disturbances. In reviewing this literature, it should be noted that hormone replacement therapy, like many other exogenously-based therapies, has been subject to constant change when new or improved hormone-derivatives become available. For a full review of the changing rationales for HRT usage from 1960 to 2000, the reader is referred to Wilkins (2002).

A single search of Medline and PsychInfo databases, using hormone replacement therapy (HRT) and mood as the keywords, elicited some 264 research articles published since 1990 dealing with this topic. The

following selection was chosen to show that research continues to explore the efficacy of HRT usage during transition in relation to psychogenic-type symptoms.

Hormone replacement therapy seeks to replace the naturally diminishing levels of oestradiol (the primary oestrogen secreted by ovarian function in premenopausal women). It can be delivered either orally, or by patches, injections or implants, or by creams or pessaries, in the form of oestrogen only or a combination of oestrogen and progesterone (Cabot, 1996). Estimates of current HRT usage in Australia are difficult to ascertain. However, in the mid-1990s, France, Schofield and Lee (1997) reported 47% of a study population of 258 middle-aged Australian women were currently using HRT, with 14% being previous users. Its use has been advocated to the general medical profession for the management of such menopausal symptoms as vasomotor instability (including hot flushes/sweats), sleep disturbances (including nocturnal flushes/sweats), negative mood and symptoms of dysphoria, urinary tract infections and incontinence; and reduction of risk of osteoporosis, coronary artery disease, cognitive dysfunction and improved longevity (Cutson & Meuleman, 2000).

In respect of its usage to reduce episodes of flushing and improve mood, a Swedish study (Collins, & Landgren, 1997) reported that approximately 55% of HRT users started treatment for relief of somatic

symptoms (eg. vasomotor symptoms of flushing), while a further 20% believed that HRT would relieve psychological symptoms associated with anxiety and depression. In a similar study of Australian women, France, et al. (1997) reported 35% of then current users gave alleviation of vasomotor symptoms as the reason for commencement of HRT, with 40% citing to improve emotional well-being as their reason for commencement of use. Interestingly, this compared to 48% of prior users citing vasomotor symptoms, with only 17% citing improvement of emotional well-being.

As early as 1977, Thomson and Oswald sought to assess the effects of hormone replacement therapy on sleep, mood and anxiety in transitional women. Using a double-blind controlled study, 34 women in early transition were given either HRT or a placebo. Sleep was monitored using EEG and mood/anxiety was rated daily using visual analogue scales. For those who had complained of insomnia, HRT did reduce the number of episodes of wakefulness, and increase the amount of REM sleep. Mood and anxiety levels were not significantly different between women in the HRT group and women in the control placebo group.

Some 20 years later, Pearce, Hawton and Blake (1995) reviewed the literature relating to the effect of HRT on psychological well-being in middle-aged women. They concluded that the literature failed to provide anything but very weak scientific support for the role of HRT in alleviating psychological symptoms in this population. Their review contrasts with

Sherwin (1996) and Brace and McCauley (1997) who concluded that the clinical literature provided evidence that oestrogen enhanced mood, psychological well-being and cognition in post-menopausal women.

Research studies continue to present differing results in terms of the effect of HRT in improving mood and quality of sleep. In 1995, Purdie, Empson, Crichton and Macdonald, using a single-blind, placebo-controlled study reported a significant improvement in psychological well-being in their HRT group, but no significant improvement in sleep quality. Their report suggested that HRT could result in measurable improvement in psychological well-being that was independent of sleep quality. In contrast, Polo-Kantola, Erkkola, Helenius, Irjala and Polo (1998) used a double-blind cross-over (HRT and placebo) study to assess the effects of HRT on sleep and mood during transition. Their results suggested an improvement in time to fall asleep and a decrease in restlessness and nocturnal awakenings within the HRT group. In reporting these results they noted that the more severe the initial insomnia was, the better HRT facilitated falling asleep. With regard to the effect of HRT on mood they reported only low strength correlations (range $\underline{r}$ = .28 -.37) between HRT usage and improvement of mood. In their 3 year longitudinal study of symptom relief in 875 North American women (45 – 64 years of age) who had achieved menopause, Greendale et al. (1998) noted no significant differences in levels of anxiety, cognitive functioning or affect between women who were treated with either oestrogen or combined oestrogen-

progesterone regimes and their untreated counterparts. However, when examining levels of anxiety and insomnia in 70 peri-menopausal Australian women (45 - 54 years of age), Boyle and Murrihy (2001) reported significantly lower self-reported levels of anxiety and insomnia in the 35 women on an HRT regime than their 35 untreated counterparts.

One possible explanation put forward for such divergence in results using single or double blind placebo trials and self-reported psychogenic symptoms is the placebo effect. Following their earlier literature review that concluded only a weak link between HRT and psychological symptoms of menopause (Pearce, et al., 1995), Pearce, Hawton and Blake (1997) undertook a placebo-controlled study designed to investigate the psychological effects of either continuation or discontinuation of HRT. After an eight week trial, they reported no difference in either psychological or psychiatric outcomes for either the treatment group (oestrogen implant) or the placebo group. They concluded that participants in both groups consistently re-requested treatment because of their belief that the treatment was assisting transition.

Pearce, et al. (1997) noted in their discussion that all their participants were currently attending a menopause clinic for continuing HRT treatment, and that some 50% had been assessed by the clinic as 'psychiatric cases' according to the Present State Examination measure used by the clinic to assess psychiatric morbidity levels. Sherwin (1996)

had also raised the issue of duration and severity of transitional symptoms of depression. In her review of literature she concludes that administration of exogenous oestrogen to women not classified as having major depression will likely improve their dysphoric mood. However, for transitional women with clinically-assessed depression, she suggests that normal dosage rates (0.625 – 1.25 mg) of conjugated oestrogen would be unlikely to be effective in alleviating their psychogenic symptoms. More recently Schleifer, Justice and de Wit (2002) sought to assess the effect on mood of oestrogen in transitional women. This study administered transdermal estradiol, a placebo, and d-amphetamine (used as a positive control) to menopausal women who were not currently undergoing HRT-assisted transition. They reported that while the d-amphetamine group exhibited stimulant effects, there was no significant difference in reported mood between those participants in the transdermal oestrogen group and those receiving the placebo patch.

While the above studies represent only a snapshot of the published literature with regard to the efficacy of HRT in relation to mood disorders and quality of sleep, it does indicate there is still a divergence of research opinion with regard to the usefulness or otherwise of hormone replacement therapy in terms of the alleviation of transitional psychogenic symptoms.

CHAPTER 3

STUDY 1

THE IMPACT OF MENOPAUSAL SYMPTOMS ON LIFESTYLE DURING MENOPAUSAL TRANSITION

Aims and Methodology

"I am going to sail on the ocean and play with the dolphins and travel with the wind and the waves" (Jo Wainer, 1998 – when discussing her attitude to her menopausal transition)

3.1 Introduction:

The overall aim of Study 1 was to explore the impact of physiological and psychological health-related issues of menopause on transitional women's lifestyles. However, particular attention was also paid to two sub-sets of symptoms, referred to as "psychogenic symptoms" and "nocturnal thermoregulatory symptoms".

All data used in Study 1 were collected from the same sample population, using the same questionnaire-based methodology. However, for ease of presentation and to avoid confusion in terminology, the Study Rationale, Aims, and Results Sections have been presented as two separate research analyses. Analysis A addressed issues related to the impact of overall menopausal symptoms on lifestyle, while Analysis B looked specifically at the effects of the two sub-sets of psychogenic and

nocturnal thermoregulatory symptoms. As both the Participant Selection/Study Procedure (see Chapter 3.3) and Measures Used (see Chapter 3.4) was common to both analyses, they have been reported as such. The results from Analysis A and Analysis B have been presented as a separate chapter (Chapter 4) with each analysis having its own Summary of Results section.

Table 3.1 explains terminology common to both Analysis A and Analysis B of Study 1.

Table 3.1: Definitions of common terms (with the appropriate abbreviations) used in Analysis A and Analysis B of Study 1

ABBREV.	DEFINITION
HSC	**Health Symptom Checklist:** A list of 33 of the most commonly reported health-related issues encountered during menopausal transition (see Appendix 3.1).
MSF	**Menopausal Symptom Frequency:** Participants' subjective opinion of the *frequency* (over a previous 14-day period) of health-related issues outlined in the Health Symptom Checklist (HSC).
MSS	**Menopausal Symptom Severity:** Participants' subjective opinion of the *severity* of impact on maintenance of normal lifestyle (over a previous 14-day period) of health-related issues outlined in the Health Symptom Checklist (HSC).
PS	**Psychogenic Symptoms:** A list of symptoms that are a sub-set of the issues listed in the HSC, namely: • Trouble Sleeping • Lack of Energy • Nervous Tension • Difficulty in Concentration • Sadness/Downheartedness
PSF	**Psychogenic Symptom Frequency:** Participants' subjective opinion of the *frequency* (over a previous 14 day period) of psychogenic symptoms, embedded in the HSC.

Table 3.1: Definitions of common terms (with the appropriate abbreviations) used in Analysis A and Analysis B of Study 1 – Continued:

ABBREV	DEFINITION
PSS	**Psychogenic Symptom Severity:** Participants' subjective opinion of the *severity* of impact on maintenance of normal lifestyle (over a previous 14 day period) of psychogenic symptoms, embedded in the HSC.
NTS	**Nocturnal Thermoregulatory Symptoms:** A list of symptoms that are a sub-set of the issues listed in the HSC, namely: • Cold sweats during the night • Hot flushes/sweats during the night
NTSF	**Nocturnal Thermoregulatory Symptom Frequency:** Participants' subjective opinion of the *frequency* (over a previous 14 day period) of nocturnal thermoregulatory symptoms, embedded in the HSC.
NTSS	**Nocturnal Thermoregulatory Symptom Severity:** Participants' subjective opinion of the severity of *impact* on maintenance of normal lifestyle (over a previous 14 day period) of nocturnal thermoregulatory symptoms, embedded in the HSC.

3.2 Rationale and Aims:

3.2.1 Analysis A:

Anecdotal evidence has suggested that while some women will, during their menopausal transition, "play with dolphins and travel with the wind and the waves" (Wainer, 1998), others will feel as if they are drowning.

Previous large-scale community-based studies of menopausal transition (McKinlay, et al., 1992, Dennerstein, et al., 1993, von Muhlen, et al., 1995) have, in the main, addressed the issue of frequency of menopausal symptoms, rather than the ways in which these symptoms impact on lifestyle during this transitional period. Some research has suggested that good or poor pre-menopausal health may be the main predictor of women's physiological and psychological health during menopausal transition (Abraham, et al., 1994, Dennerstein, 1996). However, the fact remains that not all women, regardless of their pre-menopausal health, see menopausal transition as having a negative effect on their ability to enjoy a normal lifestyle during this transitional time.

Citing the previous research of Kaplan-deNour, (1982), Murawski, et al., (1978), and Zyzanski, et al. (1981), Derogatis and Derogatis (1990) proposed that a person's individual level of psychosocial adjustment played as important a role in determining the quality of any 'illness' experience, as their physiological symptoms. Although menopausal

transition is not deemed as an 'illness' in the conventional sense of the word, many of its symptoms are health-related (see Chapter 2.1). Due to the length of transition for many women these symptoms are seen as chronic.

While intra-psychic function has frequently been described as having a number of distinct components, (eg. mood and affect, intellectual function, and memory), Derogatis (1986) argued that psychosocial adjustment was also multi-dimensional. In his opinion, the principal components of psychosocial adjustment were either composed of, or strongly related to, the salient behaviours exhibited within the workplace, the family, and during social and leisure activities. In short, roles in the psychosocial environment. According to Derogatis, the level at which any individual functioned efficiently within these various roles highly correlated with that person's own judgments concerning his or her level of psychosocial adjustment (Derogatis, & Derogatis, 1990). There is now growing evidence of a number of areas considered to be within the psychosocial domain (see Chapter 2.5) that may impact on the way in which individual women negotiate their menopausal transition.

Many studies have examined the *frequency* of menopausal symptoms. However, no studies to date have addressed the issue of the role and predictive value of psychosocial factors (including incorporating the "illness" paradigm), when assessing the *severity* of impact of a wide

range of symptoms on maintenance of a normal lifestyle during menopausal transition. Similarly, previous research has pointed to the fact that many women commence the use of hormone replacement therapy to alleviate the symptoms of menopause. Again, there appear to be no published studies that have specifically compared women using natural transition and their HRT-assisted counterparts in terms of the psychosocial/illness paradigm.

Thus, Analysis A sought to establish:

(1) Whether the symptomatic *frequency* profile of its community-based sample fitted the patterns previously reported by other community-based studies of women undergoing menopausal transition (McKinlay, et al., 1992; Dennerstein, et al., 1993, von Muhlen, et al, 1995).

(2) Whether the symptomatic *frequency* and/or *severity* profiles of participants (assessed by the 33-item HSC) were significantly different between women undergoing natural transition and those undergoing HRT-assisted transition.

(3) Whether there were significant differences in measures of psychosocial health (psychosocial factors) between women

undergoing natural transition and their HRT-assisted counterparts.

(4) Whether psychosocial factors could be used to predict the severity of impact of physiological and/or psychological health-related menopausal symptoms (from the 33-item Health Symptom Checklist) in maintenance of normal lifestyle during transition.

In the context of this study, psychosocial factors were assessed using the following measures:

- adjustment to current psychosocial environment (using the Psychological Adjustment to Illness Scale : PAIS),

- general psychological health (using the 30-item General Health Questionnaire : GHQ-30),

- perception of sleep quality (using the Pittsburgh Sleep Quality Index : PSQI),

- pre-menopausal health, defined as
    - *menstrual history (MH)*: a retrospective evaluation of the disruption caused by the monthly menstrual cycle on pre-menopausal lifestyle,
    - *pre-menstrual tension (PMT)*: the effect on mood during the late-luteal phase (4-5 days prior to each monthly bleed) on pre-menopausal lifestyle.

NOTE: The psychometric properties of the above measures are discussed in greater detail in Chapter 3.4 – Measures Used.

3.2.2 Analysis B:

As discussed in Chapters 2.3 and 2.4, previous community-based studies have shown the most frequently reported transitional symptoms to be those associated with sleep disturbances and resultant fatigue. However, thermoregulatory disturbances resulting in frequent nocturnal flushing episodes feature strongly, as do other psychogenic-type symptoms associated with anxiety, tearfulness, nervous tension, and difficulty in concentration (McKinlay et al., 1992, Dennerstein et al., 1993, von Muhlen et al., 1995).

Again, while previous research has examined the *frequency* of such symptoms, no study using a currently menopausal population comprising both natural and HRT-assisted participants, has compared the *severity* of

impact of psychogenic and/or nocturnal thermoregulatory symptoms in terms of maintenance of a normal lifestyle during transition. Nor has any study sought to assess the *predictive* value of psychosocial factors on *severity* of impact of such symptoms within this population.

Looking specifically at the subsets of psychogenic and nocturnal thermoregulatory symptoms of menopausal transition, Analysis B sought to establish:

(1) Whether the symptom *severity* profile for either the psychogenic symptom subset or the nocturnal thermoregulatory symptom subset differed significantly between participants undergoing natural transition and those undergoing HRT-assisted transition.

(2) Whether the *severity* of impact of these subsets was predicted by the same psychosocial factors as those of overall menopausal symptoms (ie: Analysis A)

3.3 Participant Selection & Study Procedure: Analyses A & B:

3.3.1 Recruitment:

Recruitment sources used were via the global e-mail network of Victoria University, Melbourne, feature articles in Fairfax community newspapers and the 'On the Spot' columns in Leader community newspapers throughout Melbourne. Leaflets detailing the study were also left at Breast-Screen Victoria offices in Melbourne. Snowball sampling of those who responded to e-mails, newspaper articles, and information leaflets was also used. However, to ensure a community sample that was not biased towards people seeking help for menopause or other health concerns, no recruitment was made at any health centre or clinic offering menopausal referral services and/or counseling. No details of the specific nature of the study, other than that the first stage was questionnaire-based and sought participation from women approximately 44 to 58 years of age and who believed they had commenced menopausal transition, were given at the time of calls for participation. Similarly, during the initial screening telephone conversations prospective participants were told only that the study would seek information on a range of menopausal symptoms.

3.3.2 Selection Criteria:

In formulating the selection criteria for the study, consideration was given to the accuracy of using self-report methods to assess menopausal status. It was acknowledged that blood tests assessing levels of such

ovarian hormones as follicle stimulating hormone (FSH) or oestrogen would provide a more specific profile of commencement of transition or interim transitional stages. The two main concerns expressed with regard to use of self-report methods have been (i) the ability of respondents to correctly assess the point at which they commenced menopausal transition and, (ii) the accuracy of using retrospective information to define their stages of transition.

With regard to the latter, Dennerstein et al. (1993) addressed the issue of the accuracy of retrospective reporting when comparing some 900 women's own beliefs of their current stage of menopausal transition with their inferred medical history. They noted that, in 71% of cases, self-reported assessments coincided with medical history. The most notable discrepancy was 13% of participants who believed they had achieved 12 consecutive months amenorrhoea, when in fact their menstrual history had shown that 12 consecutive months had yet to elapse.

To assess the inception stage of peri-menopause Brambilla, McKinlay and Johannes (1994) developed a criterion for self-reporting for use in epidemiological investigations. From data obtained using a sub-set of women (n=1,550) who had taken part in the longitudinal Massachusetts Women's Health Study (MWHS), Brambilla et al. suggested the two items that best defined the onset of menopausal transition were (a) a minimum of three months amenorrhoea, or (b) for those without amenorrhoea,

increased menstrual irregularity (ie. greater or lesser monthly bleed patterns than normal monthly bleed patterns).

The exact date at which women achieved 12 consecutive months of amenorrhoea was not seen as of primary importance in the present study, nor was there any comparative analysis between pre- and peri-menopausal participants planned for the present study. Thus, self-report measures were used to assess suitability of respondents to participant, with the Brambilla et al. (1994) criteria adopted for assessing whether they had commenced menopausal transition.

Invitations to participate in Study 1 were extended to women who were approximately 44 to 58 years of age, believed they were currently in menopausal transition, and who fulfilled the following criteria:

"Early" Transition Group:

Women who had:

(a) bleed patterns that were more frequent than normal bleed patterns,

(b) bleed patterns that were less frequent than normal bleed patterns,

(c) more than three months, but less than 12 consecutive months without a bleed.

"Mid" Transition Group:

Women who had:

(a) more than 12 consecutive months, but less than 24 consecutive months without a bleed, who were still experiencing symptoms of transition.

"Late" Transition Group:

Women who had:

(a) more than 24 consecutive months without a bleed, but who were still experiencing symptoms of transition,

(b) if, having undergone a simple hysterectomy, were still experiencing symptoms of menopausal transition.

Women who had undergone a simple hysterectomy (group b above) have often been excluded from community-based studies of menopausal transition, although it is known that they still experience menopausal symptoms due to continuing ovarian function (see Chapter 1.1.3). There appeared to be no convention for defining their transitional stage, when such definition was based on date of last bleed. A decision was therefore taken in this study, to assign participants who had undergone simple hysterectomies to the "late transitional" group. The rationale behind this assignment was that the "late" transitional group most closely fitted their lack of bleed profile, and therefore lack of on-

going concerns with regard to possible disruption or distress caused by the uncertainty of on-going bleed patterns.

As previously stated, women were not excluded from this study on the basis of their previous or current use hormone replacement therapy (HRT). However, to correctly assess their menopausal status of women who had recently used HRT, medical advice was sought from an *ad hoc* advisory group of General Practitioners (GPs) from three local medical practices. The GPs were given an outline of the study criteria and aims, and were then asked to assess in their opinion, the longevity within the hormonal system of various HRT preparations that they prescribe. Based on their advice the following selection criteria was used to establish 'natural' or 'HRT-assisted' transition:

(a) Participants who met the age criteria, but had not used HRT during the six weeks prior to request for participation, and did not intend to re-use during the following six-month period, were classed as undergoing **'natural'** transition,

(b) Participants who were currently using HRT and intended to continue that use were classified as undergoing **'HRT-assisted'** transition.

(c) Women who had ceased HRT use less than six weeks prior to participant selection, or had ceased but were not sure whether they would recommence within the following six month period were excluded from participation selection.

Some 130 women within the age group initially responded to the call for study participants. After an initial telephone screening conversation to ascertain what they believed to be their current transitional status and whether or not they were currently being treated for severe depressive episodes, 101 women fitted the selection criteria and were invited to participate (see Chapter 4.1 for demographic information). Women were excluded if they did not meet the age criteria, menopausal criteria, or if they were currently undergoing or seeking medical help for major depressive episodes occurring during their menopausal transition. To avoid misclassification of women using medically prescribed HRT with women using non-prescription therapies, women were asked whether their HRT had been prescribed by their medical practitioner. All women using medically prescribed HRT were allocated to the HRT-assisted group. Women using non-prescription based therapies were allocated to the natural transition group.

3.3.3 Study Procedure:

Each of the 101 women who fitted the study criteria were sent the following documentation:

- a plain language statement giving details of Study 1 and briefly outlining Study 2 (Melatonin Secretion Levels and/or Rhythms within a Menopausal Population),

- Two questionnaire booklets (see Chapter 3.3 for details and psychometric properties of questionnaires contained in the booklets),

- a consent to participate in Study 1 form (contained in Questionnaire Booklet 1),

- a reply-paid envelope for return of questionnaire booklets.

All participants were informed that the study had the approval of the Human Ethics Committee of Victoria University, Melbourne. They were also informed of the voluntary nature of Study 1, and that they had the right to withdraw at any time during the study. To ensure confidentiality, each participant was given a code number that appeared on all the questionnaires included in their study package. A 'consent to participate' form was included in the questionnaire package. However participants were informed in writing this would be detached on receipt of completed questionnaires and stored separately. The questionnaire instruction form for Study 1 also included a section informing participants that a sub-sample of women would be invited to participate in Study 2. Women who

did not wish to be approached for Study 2 were asked to indicate accordingly on this form.

On receipt of fully completed questionnaires, the consent to participate form was detached and stored in a separate file. Where returned questionnaires were not fully completed (N = 7), these participants were informed and the incomplete questionnaire(s) were returned to them together with a reply-paid envelope for completion. Fully completed questionnaires were then scored in accordance with appropriate scoring procedures (see Chapter 3.4 – Measures Used) and the raw data was entered into Statistical Package for Social Science (SPSS) – Version 10 for statistical analysis.

3.4 Measures Used – Analysis A and B:

Measures used in Study 1 were divided into two questionnaire booklets. Because of the number and complexity of these questionnaires, the questionnaire instruction form advised participants to complete Booklet 1 and Booklet 2 on two separate days. The following two sections list the questionnaires used in Study 1 and, where applicable, detail their psychometric properties. Pro-forma questionnaire booklets can be found in Appendix 3.2)

3.4.1 Menopause Questionnaire Booklet 1 (MQB-1):

MBQ-1 contained the following:

3.4.1.1 Consent Form for Subjects Involved in Research:

A 'consent to participate' in research form approved by the Human Ethics Research Committee of Victoria University, Melbourne. Upon receipt of completed questionnaires, this document was detached and stored separately, to ensure confidentiality of participant information.

3.4.1.2 Health Symptom Checklist (HSC):

The HSC contained a list of 33 physiological and psychological health issues related to menopausal transition. Participants were required to only record information for those symptoms they had actually experienced during the previous two-week period. For each symptom they were asked to record frequency and severity of impact on lifestyle. Frequency was recorded as the number of days they believed they had experienced any symptom in the prior 14 days. Severity of impact of each symptom on lifestyle over that two-week period was assessed using a simple 0 to 3 Likert scale. If the experienced symptom had no impact on lifestyle no score was recorded. Minor irritation was designated a score of 1, while interfering with lifestyle was scored as 2. If the symptom had a major effect on lifestyle it received the maximum score of 3.

The Health Symptom Checklist originated from data gathered during the early stages of the Melbourne Women's Midlife Health Project (MWMHP). Based on the 22 most commonly reported menopausal health-related symptoms from the Massachusetts Women's Health Study

(McKinlay, et al., 1992) some 2,000 Australian women took part in a cross-sectional study designed, in part, to describe the frequency of their health-related symptoms during menopausal transition (Dennerstein, et al., 1993). As a result of information gained during their early studies, the MWMHP study expanded the initial 22-item checklist to one containing 33 health-related symptoms (HSC) for their longitudinal study of mid-life women. At the time of data collection for Study 1, the then current MWMHP project leader, Janet Guthrie, was kind enough to give permission for use of their 33-item health-related symptom checklist in this study.

3.4.1.3 Pre-Menopausal & Menopausal Information Form:

This short questionnaire was designed to assess:

- participants' belief of their current transitional status, their past and present HRT usage,

- menstrual history (MH) - a retrospective evaluation of the level of disruption caused to their normal lifestyle by their pre-menopausal menstrual cycle ,

- pre-menstrual tension (PMT) - the effect, if any, during the late-luteal period (4-5 days prior to commencement of monthly pre-menopausal monthly bleed) on their normal mood patterns.

Menstrual History (MH) was coded on a Simple 1 – 3 point Likert scale where, 1 = menstruation did not cause any disruption to normal lifestyle; 2 = menstruation caused occasional problems; and 3 = menstruation caused significant disruption to normal lifestyle.

Pre-menstrual tension (PMT) was similarly assessed. A score of 1 equated to no difference in mood during the four to five days before a monthly bleed (late-luteal phase) than during the rest of the month; a score of 2 represented a mild deterioration in mood during this phase; and 3 designated a significant worsening in mood during the late-luteal phase.

3.4.1.4 Pittsburgh Sleep Quality Index (PSQI):

The Pittsburgh Sleep Quality Index was developed by Buysse, Reynolds, Monk, Berman and Kupfer (1988), as a global measure of subjective sleep quality within clinical populations, and for use in sleep-related research activities. As a self-rating instrument, the PSQI was designed to assess overall sleep quality during a retrospective period of one month. The sum of its seven component scores (covering subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleep medication, and daytime dysfunction) yielded a global score ranging from zero to 21.

During its development, the PSQI's clinometric properties were assessed over an 18 month period using healthy, depressed and sleep

disordered participants. Reliability was established by test-retest, with no significant differences between trials on both the global and individual component scores within a non-clinical population. Using Cronbach's alpha, an overall reliability coefficient of 0.83 indicated a high degree of internal consistency for each of the seven component scores.

Based on their clinical trials, Buysse, et al (1988) recommended use of a global cut-off score of five or less as indicative of good subjective sleep quality. In their opinion, a score greater than five indicated severe difficulties in at least two of the component areas, or moderate difficulty in more than three areas.

3.4.2 Menopause Questionnaire Booklet 2 (MBQ-2)

While MQB-1 contained questionnaires that related to menopausal symptoms, and pre-menopausal history, the questionnaires in MQB-2 were chosen to assess general psychological health and psychosocial factors during transition.

3.4.2.1 General Health Questionnaire (GHQ):

First issued in 1972 (Goldberg) the GHQ was initially developed as a self-administered screening test, aimed at detecting psychiatric disorders within community and non-psychiatric clinical settings. As an easy to administer questionnaire, the GHQ did not require a subjective assessment to be made by those administering it. As its purpose was to assist in

detecting forms of psychiatric disorders that led to a person's presence in a medical, or community clinic, its main focus was on the psychological components of ill health.

While the initial GHQ had 60 items, three shorter versions were subsequently developed (the GHQ-12, the GHQ-28 and the GHQ-30). Of these three the GHQ-12 and the GHQ-30 have had items referring to physical health removed, whereas the GHQ-28 still has questions pertinent to physical as well as psychological health. As the version most widely validated for use in general studies, and one focusing on psychological issues, the GHQ-30 was chosen for this study. Using countries as diverse as Italy, Iceland, Scotland, North America, Jamaica, Ireland, Canada, Mexico, England, Austria and Australia, the GHQ-30 has been shown to be sensitive to depression (88%) and panic disorders (76%). During its validation, 29 studies were undertaken in various countries, with a median value for sensitivity shown as 81%. Of the 29 studies, 21 yielded values within ten percent of this figure.

The four-point GHQ response scale can be scored in a number of different ways. Discriminant function analysis can be used, where separate weights are computed for each item. Alternatively it can be treated as a bimodal response scale (0-0-1-1), where only pathological deviations from normal allocates possession of the item. It can also be scored using a modified Likert (0-0-1-2) or by using a simple Likert (0-1-2-

3) scale. When outlining alternative scoring methods, the User's Guide for GHQ-30 rejected discriminant function analysis, with its notion of assigning separate weights, as being laborious and offering no clear advantage over other methods. Comparison of results using the other methods, showed the modified Likert to be inferior to either the bimodal or simple Likert. The Guide noted that, while the bimodal scale considered only the number of symptoms and could be seen as an 'area' measure, rather than encompassing both 'area' and 'intensity', the overall misclassification rate using the bimodal method was only 0.7% less (13.3%) than using the simple Likert (12.6%). As the purpose the GHQ-30 in the present study was to obtain an overall general psychological health score for each participant, rather than for initial clinical case identification, the slightly more accurate simple Likert scale scoring method (0-1-2-3) was used for each response.

The extent to which any questionnaire score can detect psychological or psychiatric disturbance presupposes, according to User's Guide for GHQ-30, an axis of such disturbance upon which any individual can be placed. However, it argued that, as there was no clear dichotomy between 'normal' and 'disturbed cases' in the sense of a specific point where normality ends and psychological [psychiatric] disturbance commences, the most preferred method of distinguishing between good and poor psychological health using the GHQ was that of the 'best threshold score'. Using the simple Likert scoring method for the GHQ-30,

the best threshold score of 39, quoted in the User's Guide, was used in this study as the marker between good and poor psychological health.

3.4.2.2 Psychosocial Adjustment to Illness Scale (PAIS):

This self-report measure was developed by Derogatis and Lopez (1983) as an easy to administer, inexpensive tool, that would allow individuals to express their own unique 'illness' experiences, without being subjected to an interview situation or errors due to rater bias (Derogatis, 1986). While acknowledging that there were numerous factors that related to issues of psychosocial adjustment, the self-report version of PAIS was designed to assess several principal psychosocial domains, shown to be central when considering issues of adjustment to a medical condition or illness (Derogatis, 1986).

The seven domains addressed in the PAIS are:

Health Care Orientation: Primarily concerned with the respondent's attitude to health care in general, their perception of the quality of health care information and health care professionals; and expectations of how their medical condition or illness is being addressed.

Vocational Environment: Assesses the impact that the medical condition/illness might have on normal function within either the workplace, school or performing tasks within the home.

Domestic Environment: Designed to assess problems arising from the way in which the immediate family adapted to the medical condition/illness, including the quality of relationships and communication.

Sexual Relations: Provides a quantitative estimate of any changes in either sexual functioning or sexual relationships.

Extended Family Relationships: Measures the disruption or derangement in relationships within the extended family circle, including such issues as loss of interest in interacting, changes in communication and quality of relationships.

Social Environment: Assesses the degree of which an individual had changed his or her social or leisure activities since the onset of the medical disorder/ illness.

Psychological Distress: Designed to measure the effects of such issues as anxiety, depression, hostility, self-esteem, body image and inappropriate guilt.

Originally normed for use within study populations suffering from a variety of cancers, cardiac conditions, kidney failure requiring dialysis, and acute burns (cited in Derogatis 1986), PAIS has subsequently been used to assess the psychosocial health of, among others, diabetics (cited in

Derogatis, & Derogatis, 1990), sufferers of chronic pain, such as musculo-skeletal pain (Weir, Browne, Tunks, Gafni, & Roberts, 1996) and narcolepsy (Bruck, 2001).

Although the PAIS has not previously been used to investigate the relationship between psychosocial adjustment and the impact of menopausal symptoms on lifestyle within a transitional population, it has been used to assess the effects of HRT and counseling on the psychosocial adjustment of women in mid to late transition (Roberts, Chambers, Blake, & Webber, 1992). Using the definition of 'illness' as the human experience of loss, dysfunction or concern, and 'symptom' as interruption, inconvenience, or health worry (Brenner, & Wrubel, 1989, cited in Roberts, et al., 1992), Roberts, et al. argued that, in this context, illness was the human response to the symptom.

Roberts, et al. (1992) believed that, with regard to menopausal transition, the PAIS could be successfully used to assess psychosocial adjustment, if the word 'illness' referred to in the PAIS questions, was replaced by the word 'menopause'. Cronbach's alpha, used to determine internal consistency within this population, gave the following domain alphas: Health Care Orientation = 0.65, Vocational Environment = 0.86, Domestic Environment = 0.88, Sexual Relations = 0.81, Extended Family Relationships = 0.55, Social Environment = 0.95, and Psychological Distress = 0.93.

To ensure participants in the present study did not misconstrue or misinterpret the use of the word 'illness' in the PAIS, the questionnaire was accompanied by a statement outlining why the PAIS was being used, and asking participants to substitute the words 'menopausal transition' or 'menopause' for 'illness' when answering the various questions (see Appendix 3.2, MQB-2, p 3).

CHAPTER 4

RESULTS OF STUDY 1

ANALYSES A & B

4.1 Participant Demographics:

Seventy-one women (70.3%) of the 101 women who fitted the selection criteria returned fully completed questionnaires, showing a high first response rate for a postal questionnaire-based study. Their ages ranged from 43.5 years (N=1) to 57.9 years (N=1), with a mean age of 50.02 years (SD = 3.52 years) and a median age of 50.00 years.

Based on their self-classification of current transitional status (see Chapter 3.3.2), 41 of the 71 participating women believed they were in early transition (M = 48.97 years, SD = 3.54 years), seven classified themselves as mid-transitional (M = 51.23 years, SD = 3.65 years), and 23 women believed they were in late transition (M = 51.51, SD = 2.88). Of the 23 women in the late menopausal group, four were women who had undergone simple hysterectomies, but had intact ovaries. Fifty-one (72%) of participants were currently living with a partner, while 20 (28%) were living independently of a partner. Other pertinent pre-menopausal and menopausal characteristics of participants who took part in Study 1 are shown in Table 4.1.

Table 4.1: Pre-menopausal and menopausal characteristics of participants in Study 1:

(a) Method of Menopausal Transition:	Number	Rounded Percentage
Never used hormone replacement therapy	38	54%
Past users of hormone replacement therapy	12	17%
Present users of hormone replacement therapy	21	30%

- **Note:**

  Women who have never used, or are not currently using hormone replacement therapy have been combined into the Natural Transition Group for the remainder of the data analysis

(b) Current Menopausal Status:	HRT		Natural		Total	
	No.	%	No.	%	No.	%
Early Transition (irregular bleed or 3-11 mths without bleed)	8	38%	33	66%	41	58%
Mid Transition (>11 but < 24 mths without bleed)	0	0%	7	14%	7	10%
Late Transition (24+ mths with remaining symptoms)	13	62%	10	20%	23	32%

(c) Menstrual History (MH):

No Disruption		Some Disruption		Severe Disruption	
HRT	Natural	HRT	Natural	HRT	Natural
10(48%)	20(40%)	7(33%)	20(40%)	4(19%)	10(20%)

(d) Pre-Menstrual Tension (PMT):

No Mood Change		Mild Change		Severe Change	
HRT	Natural	HRT	Natural	HRT	Natural
5(24%)	10(20%)	13(62%)	23(46%)	3(14%)	17(34%)

4.2 Results – Analysis A

4.2.1 Menopausal Health Symptom Frequency:

The ten most frequently reported symptoms from the Health Symptom Checklist (HSC) experienced by participants in the two-week period prior to their involvement in the study are shown in Table 4.2. Four of the five symptoms within the psychogenic symptom cluster were in this frequently reported group (trouble sleeping, lack of energy, feeling sad/downhearted, difficulty in concentration), as were some thermoregulatory symptoms (diurnal and nocturnal hot flushes/sweats) and several skeletal symptoms (backaches, general aches/stiff joints, headaches/migraines).

Table 4.2: Ten most frequently reported symptoms, shown as rounded percentages of respondents reporting incidence of symptoms in the previous two-week period.

Symptom*		HRT (n=21)	Natural (n=50)	All (n=71)
p	Trouble sleeping	76%	80%	79%
t	Hot flushes/sweats at night	67%	72%	70%
p	Lack of energy	52%	68%	63%
s	Aches/stiff joints	62%	64%	63%
p	Feeling Sad and Downhearted	57%	64%	62%
s	Headaches/Migraines	57%	60%	59%
p	Difficulty in concentration	43%	60%	55%
t	Hot flushes/sweats at day	52%	56%	55%
s	Backaches	48%	58%	55%
	Skin irritation(dryness/crawling)	38%	54%	49%

* where: 'p' denotes psychogenic symptoms;
's' denotes skeletal symptoms,
't' denotes thermoregulatory symptoms.

A comparison of obtained frequencies from this study (Table 4.2) and that of the larger Melbourne Women's Midlife Health Project (MWMHP) cross-sectional study (n = 904), shows a difference in order of reported frequency, but similar results in terms of the top ten most frequently cited transitional symptoms (see Appendix 4.1 for comparative table).

4.2.2 Impact of Menopausal Symptom Severity (MSS) on Maintenance of a Normal Lifestyle during Transition:

In addition to recording the frequency of health-related transitional symptoms, the 33-item HSC allowed participants to rate the degree to which they believed the severity of each symptom had impacted on their ability to maintain a normal lifestyle during transition (MSS). Participants assigned a score from zero (no disruption) to three (major disruption) for each of the 33 health-related symptoms that they had experienced in the two-week period prior to completing the HSC. Initially these scores were simply summated such that a maximum possible score for each symptom across all 71 participants was 213 (71 x 3) and the minimum score was zero.

Using these sum statistics, Table 4.3 shows the ranking, in order of descending value, of the cumulative severity scores assigned to each symptom on the HSC.

Table 4.3: Cumulative severity symptom scores (MSS) assigned to each of the 33 health-related items contained in the health symptom checklist (HSC) (N=71):

Symptom	Sum Statistic	Stat. Mean	Std.Error
Trouble Sleeping	121	1.70	0.13
Hot Flushes/Sweats at Night	93	1.31	0.13
Lack of Energy	90	1.27	0.14
Feeling Sad/Downhearted	85	1.20	0.13
Headaches or Migraines	75	1.10	0.12
Hot Flushes/Sweats at Day	74	1.04	0.14
Aches or Stiff Joints	70	0.99	0.11
Backaches	66	0.93	0.12
Nervous Tension	64	0.90	0.13
Difficulty in Concentration	63	0.89	0.11
Skin Irritation (crawling/dryness)	55	0.77	0.12
Problems with Urine Control	53	0.75	0.11
Dry Vagina	50	0.70	0.12
Diarrhoea or Constipation	50	0.70	0.11
Swelling of Body Parts	37	0.52	0.07
Shortness of Breath on Exertion	31	0.44	0.07
Dizzy Spells	30	0.42	0.06
Tingling/Pins &Needles in Hands/Feet	30	0.42	0.06
Breast Soreness/Tenderness	29	0.41	0.06
Rapid Heartbeat/Palpitations	27	0.38	0.06
Upset Stomach	26	0.37	0.07
Dry Eyes	25	0.35	0.06
Cold Sweats at Night	20	0.28	0.07
Sore Throat	18	0.25	0.05
Persistent Cough	17	0.24	0.04
Loss of Appetite	15	0.21	0.06
Chest Pain on Exertion	14	0.20	0.04
Dry Nose or Mouth	14	0.20	0.05
Cold Sweats at Day	13	0.18	0.05
Shortness of Breath at Rest	9	0.13	0.04
Troublesome Vaginal Discharge	9	0.13	0.03
Discomfort on Passing Urine	6	0.06	0.04
Bladder Infection Problems	6	0.06	0.04

Sum statistic data reported in Table 4.3 show the cumulative sum effects of the impact of menopausal symptoms on maintenance of a normal lifestyle within this transitional population. However, not all women rated symptoms as causing major disruption (ie. debilitating). Table 4.4 shows the top ten symptoms in terms of the rounded

percentage of women who recorded the maximum score of three (major disruption) and indicates that many women did not report symptoms as debilitating.

Table 4.4 Percentage of women ranking symptom severity as having a major disruption on maintenance of a normal lifestyle during transition.

	Health-Related Symptom	Percentage of participants ranking symptom as major disruption (=3)
1.	Trouble sleeping	31%
2.	Lack of energy	23%
3.	Hot flushes/sweats at night	21%
4.	Feeling sad or downhearted	17%
5.	Hot flushes/sweats during the day	17%
6.	Nervous tension	14%
7.	Headaches or migraines	9%
8.	Backaches	9%
9.	Difficulty in concentration	7%
10.	Aches or stiff joints	6%

4.2.3 Comparison of Menopausal Symptom Severity and Psychosocial Factor Values for Natural and HRT-Assisted Participants:

Single factor Multivariate Analysis of Variance (MANOVA) was used to determine whether any significant differences existed between natural and HRT-assisted participants with regard to both menopausal symptom severity (MSS) and values obtained from psychosocial measures (MH, PMT, PSQI, GHQ-30, PAIS-T). Results showed no significant main

difference ($F(64)= 1.01$, $p = .427$) between natural or HRT-assisted participants for the mean values obtained (see Table 4.5 for means, standard deviations, and univariate statistics).

As there were no significant differences between scores of those women undergoing natural transition and those using HRT, the scores of the two groups were combined for analysis of impact of overall menopausal symptom severity, and predictors of maintenance of a normal lifestyle during transition.

Table 4.5: Descriptive and inferential statistics for measures used for natural and HRT-assisted transitional participants

Measure Used	Status	N	Mean	SD	F-Value	p-value
Menopausal Symptom Severity (MSS)	Natural	50	19.72	10.53		
	HRT	21	18.86	11.69	0.09	.761
Menstrual History (MH)	Natural	50	1.80	0.76		
	HRT	21	1.71	0.78	0.18	.668
Pre-menstrual Tension (PMT)	Natural	50	2.14	0.73		
	HRT	21	1.90	0.62	1.67	.201
Sleep Quality (PSQI)	Natural	50	9.48	3.80		
	HRT	21	8.62	4.33	0.70	.406
General Psychological Health (GHQ-30)	Natural	50	33.98	12.89		
	HRT	21	39.10	16.43	1.97	.165
Psychosocial Adjustment (PAIS-T)	Natural	50	37.18	20.76		
	HRT	21	37.57	17.82	0.01	.940

4.2.4 Predictive Value of Psychosocial Factors when related to Menopausal Symptom Severity:

In this analysis, the main area of interest was in establishing the psychosocial factors that predicted menopausal symptom severity in terms of its impact on maintenance of a normal lifestyle during transition. A stepwise linear regression model was used, with menopausal symptom severity (MSS) scores being the dependent variable. The predictor variables were scores derived from Psychosocial Adjustment to Illness Scale (PAIS-T), General Health Questionnaire (GHQ-30), Pittsburgh Sleep Quality Index (PSQI), Menstrual History Questionnaire (MH) and Pre-Menstrual Tension Questionnaire (PMT).

As can be seen in Table 4.6, only PAIS-T, PSQI and PMT were entered into the model as having a predictive value in terms of maintenance of a normal lifestyle during transition (MSS).

Table 4.6: Predictors of impact of menopausal symptom severity (MSS) on maintenance of a normal lifestyle during transition

Variable	R Square	R Square Change	F Change	Sig.F Change
PAIS-T	.286	.286	27.65	.000
PSQI	.436	.150	18.11	.000
PMT	.482	.045	5.87	.018

R^2 values show that 28.6% of the variance in MSS was accounted for by total scores from the Psychosocial Adjustment to Illness Scale (PAIS-T). Global sleep quality (PSQI) accounted for a further 15.0% of variance. Prior recollection of the effects of pre-menstrual tension on mood (PMT), while included in the model, only accounted for a further 4.5% of the variance. General psychological health (GHQ-30) and Menstrual History (MH) were excluded as making no significant contribution to the model.

4.2.5 Psychosocial Adjustment (PAIS):

Before further analysis, the internal consistency of the seven PAIS domains, with regard to this menopausal population was tested using Cronbach's alpha. Results showed a reliability coefficient of 0.83. As the cut-off for Cronbach's scale is 0.70, internal reliability for this sample population was established for the PAIS-T.

Using the criteria established by Roberts et al. (1992) PAIS-T scores of 35 or less represented good psychosocial adjustment, scores of between 36 and 50 showed fair psychosocial adjustment, and scores of more than 50 were deemed to show poor psychosocial adjustment. Table 4.7 shows means, standard deviations and range for the 71 participants, when classified into good, fair and poor psychosocial adjustment categories as represented by PAIS-T.

Table 4.7: Means, standard deviations and range for participants classified as having good, fair and poor psychosocial adjustment (PAIS-T)

Category	No.	% of Participants	Mean	SD	Range
Good	35	49%	21.40	7.47	5 – 34
Fair	21	30%	41.95	4.54	35 – 50
Poor	15	21%	67.87	11.48	54 - 89

Independent t-tests reported no significant mean differences between participants in terms of method of transition (natural/HRT-assisted) when scores were categorised into good, fair and poor groups (Table 4.8)

Table 4.8: Descriptive and inferential statistics for PAIS-T scores (natural and HRT-assisted participants) when classified by good, fair and poor psychosocial adjustment

PAIS-T Category	Method of Transition	No.	Mean	SD	t-value(df)	p-value
Good	Natural	25	22.28	10.93		
	HRT	10	24.00	5.70	0.470 (33)	.642
Fair	Natural	15	41.40	11.10		
	HRT	8	42.00	4.28	0.146 (21)	.885
Poor	Natural	12	67.08	10.57		
	HRT	3	71.00	17.00	0.515 (13)	.615

A subsequent Chi-Square for Independence showed no significant association between method of transition and PAIS-T category membership, with Chi-Square(2,N=71) = .969, $\underline{p}$ = .616. However, it should be noted that one cell violated the minimum expected count of 5.

When all participant scores were combined for each PAIS domain, overall mean scores for PAIS showed Health Care Orientation as being of

the greatest concern to all participants regardless of their level of psychosocial adjustment (see Table 4.9 for means and standard deviations, where higher scores indicates more problematic).

Table 4.9: Means and standard deviations for individual PAIS domains, where good, fair and poor related to PAIS-T scores

Domain	Good (n=35)		Fair (n=21)		Poor (n=15)		Total (n=71)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Health Care Orientation	7.85	3.06	10.38	3.99	12.40	3.07	9.56	3.79
Vocational Environment	1.94	1.61	3.67	1.93	4.93	2.55	3.08	2.26
Domestic Environment	1.66	1.88	6.24	2.96	12.20	3.95	5.24	4.94
Sexual Relations	3.14	3.34	5.95	4.49	9.07	4.54	5.23	4.56
Extended Family Rel'ships.	0.43	0.92	2.05	2.11	6.20	4.69	2.13	3.33
Social Environment	l.03	1.92	4.86	3.29	9.87	2.97	4.03	4.32
Psychological Distress	5.40	2.58	8.81	2.91	13.33	4.50	8.08	4.40

To ascertain which of the seven individual PAIS domain scores contributed most variance toward overall psychosocial adjustment (PAIS-T), a one-sample Kolmogorov-Smirnov (2-tailed) test was run on PAIS-T to establish variance and test suitability. Mean distribution was shown as normal ($p = 0.432$). As the results of the Kolmogorov-Smirnov test showed a normal distribution of results, a normal enter method regression was used to establish which of the seven domain variables from the PAIS-T contributed most toward the overall level of psychosocial adjustment. Examination of the standardised regression coefficients (beta) showed the most important predictor of overall psychosocial adjustment was the

Domestic Environment domain, followed closely by the Psychological Distress domain (see Table 4.10).

Table 4.10: Standardised regression coefficients for the seven PAIS Domains

PAIS Domain	Standardised Coefficient (beta)
Domestic Environment	0.265
Psychological Distress	0.245
Sexual Relations	0.219
Social Environment	0.204
Health Care Orientation	0.198
Extended Family Relationships	0.123
Vocational Environment	0.124

4.2.6 Global Sleep Quality (PSQI):

Analysis of data from the Health Symptom Checklist showed trouble sleeping as the most frequently reported transitional symptom (see Table 4.2). Some 79% of participants had noted sleep problems during the previous two-week period, with 31% giving the maximum score of three (= major disruption) to the impact of their sleep problems on the maintenance of their normal lifestyle.

Although not the main predictor of good transitional health, global sleep quality as measured by the PSQI still appeared as a significant predictor, (15% of variance) of the impact of severity of menopausal symptoms on lifestyle during menopausal transition (MSS). As outlined in

Chapter 3.4.1.4, Buysse, et al. (1988) used a PSQI cut-off score of greater than five to signify severe problems in two of the seven global sleep component areas, or moderate problems in three or more of the seven component areas, with a score of five or less designating good global sleep quality.

Of the 71 participants in Study A, 58 (81.7%) recorded global sleep scores of greater than five (Mean = 10.43, SD = 3.30) while 13 women recorded global sleep scores of five or less (Mean = 3.85, SD = 1.00). As previously reported, there was no significant difference (p=>.05) between global sleep quality scores of women undergoing natural transition and those undergoing HRT-assisted transition (Table 4.5).

The PSQI does not provide graduated cut-off scores regarding the severity of sleep quality problems, other than to state that scores of five or greater indicate severe problems in at least two sleep domains, or moderate problems in at least three sleep domains. To allow further examination of PSQI results, participants with scores of less than five were classified as good sleepers (N=13). The 58 participants who recorded global scores greater than five were arbitrarily re-classified as fair sleepers (scores of six to nine, N=26) or poor sleepers (scores of 10 or greater, N= 32). Means and standard deviations for the three PSQI groups are shown in Table 4.11.

Table 4.11: Means and standard deviations for global PSQI scores of participants classified as good, fair and poor sleepers

PSQI	Status	N	Mean Global PSQI Score	SD
Good	Natural	6	3.50	1.05
	HRT	7	4.14	0.90
Fair	Natural	20	7.40	1.27
	HRT	6	7.83	1.17
Poor	Natural	24	12.71	2.30
	HRT	8	13.13	2.85

Chi Square for Independence was then used to assess whether there was any significant association between menopausal status (natural or HRT-assisted) and global sleep quality (PSQI: good, fair, poor). Results of the Chi Square showed no significant association between menopausal status and global sleep quality, with Chi Square (2, N=71) = 4.525, $\underline{p}$ = .104.

4.2.7 Summary of Results from Analysis A:

- The menopausal symptom *frequency* profile (MSF) obtained for this participant sample was in line with *frequency* profiles obtained in previous large-scale community-based studies.

- Four of the five psychogenic symptoms and one of the two nocturnal thermoregulatory symptoms listed in the 33-item HSC featured in the top ten most *frequently* reported symptoms in this study.

- Trouble sleeping was the highest ranked of the 33 items in the HSC in terms of overall *severity* of impact on maintenance of a normal lifestyle during transition, with nocturnal hot flushes/sweats ranked second highest.

- In terms of major disruption (ie. maximum score of three), 31% of participants reported that trouble sleeping had a major impact on their ability to maintain a normal lifestyle during transition. However, only 21% of women ranked the occurrence of nocturnal hot flushes/sweats as having the maximum impact (score of three) on their ability to maintain a normal lifestyle.

- There was no statistically significant difference between participants using natural transition and those using HRT-assisted transition, in terms of:

    - menopausal symptom severity scores (MSS)
    - menstrual history (MH)
    - pre-menstrual tension (PMT)
    - global sleep quality (PSQI)
    - general psychological health (GHQ-30)
    - psychosocial health (PAIS-T)

- Stepwise multiple regression analysis revealed psychosocial health (assessed by PAIS-T) as contributing the greatest amount of predictor variance (28.6%) in terms of the impact of menopausal symptom *severity* (MSS) on maintenance of a normal lifestyle during transition. Global sleep quality (PSQI) contributed a further 15% of variance, with effect of pre-menstrual tension contributing 4.5%.

- Of the seven domains of psychosocial health measured by the PAIS, health care orientation was seen as the most important issue by all women, regardless of their assessed level of psychosocial adjustment. However, the domestic environment domain contributed most toward total PAIS-T variance.

- With regard total psychosocial adjustment scores (PAIS-T), there was no significant association between method of transition (natural or HRT-assisted) and level of adjustment (good, fair or poor).

- With regard to global sleep scores (PSQI), there was no significant association between method of transition (natural or HRT-assisted) and global sleep category (good, fair or poor).

4.3 Results: Analysis B

Analysis A examined the effects of overall menopause symptoms that originated from the 33-item Health System Checklist (HSC). Analysis B, while using the same participant data, examined two sub-clusters of HSC symptoms. The first sub-cluster comprised the five psychogenic symptoms (trouble sleeping, lack of energy, feeling sad/downhearted, difficulty in concentration, and nervous tension). The second sub-cluster comprised two nocturnal thermoregulatory symptoms (hot flushes/sweats at night, cold sweats at night).

4.3.1 Psychogenic Symptoms:

As reported in Analysis A (Table 4.2), of the five psychogenic symptoms embedded in the 33-item HSC, trouble sleeping, lack of energy, sadness/downheartedness, and difficulty in concentration were cited in the top ten most *frequently* experienced symptoms (MSF). The fifth symptom, nervous tension, was ranked at number eleven. All five psychogenic symptoms were ranked in the top ten symptoms in terms of impact of *severity* of symptoms on maintenance of normal lifestyle during transition (MSS) Table 4.3). As can be seen in Figure 4.1, there were similar percentages of both natural and HRT-assisted participants' psychogenic symptom severity scores for each of the five psychogenic symptoms.

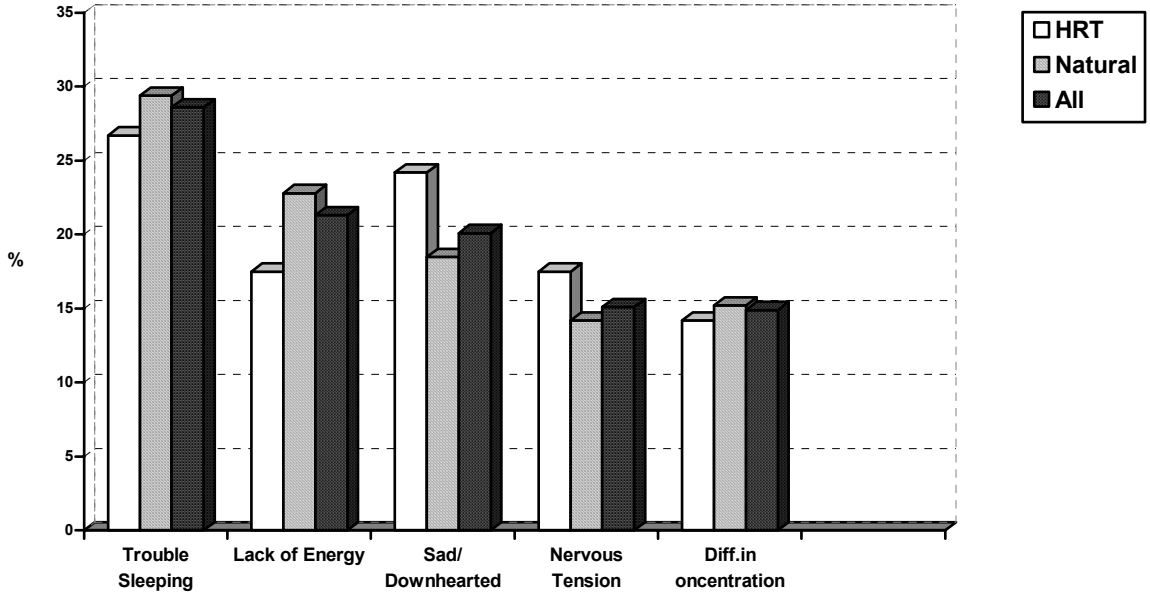

Figure 4.1: Psychogenic domain severity scores shown as a percentage of total psychogenic symptom severity scores for natural and HRT-assisted participants

An independent t-test, with transitional status (natural or HRT-assisted) as the independent variable and total psychogenic symptom severity scores (PSS) as the dependent variable confirmed there was no statistically significant difference ($\underline{p}$ =>.05) between participants using natural transition (N=50, M=5.67, SD=3.71) and those using HRT (N =21, M=6.08, SD=3.67). Scores for both groups were therefore again combined for predictive statistical analysis.

4.3.2 Predictive Value of Psychosocial Factors when Related to Psychogenic Symptom Severity:

As in Analysis A, a stepwise linear regression model was used to establish the predictive value of psychosocial factors on maintenance of a normal lifestyle during transition. The total psychogenic symptom severity score (PSS) was used as the dependent variable and scores on the PSQI, GHQ-30, PAIS-T, MH and PMT, were again used as the predictor variables.

In this model, general psychological health (GHQ-30 score) was shown to be the main predictor variable, accounting for 40.2% of the explained variance. The effect of pre-menstrual tension on mood (PMT) accounted for a further 9.3% of variance, with global sleep quality (PSQI) and psychosocial health (PAIS-T) adding a further 5.4% and 3.0% respectively (see Table 4.12).

Table 4.12: Predictors of impact of psychogenic symptom severity on maintenance of a normal lifestyle during transition

Variable	R Square	R Square Change	F Change	Sig.F Change
GHQ-30	.402	.402	46.34	.000
PMT	.495	.093	12.49	.001
PSQI	.548	.054	7.97	.006
PAIS-T	.579	.030	4.77	.033

A previous research study (Dennerstein, et al., 1997) had reported that general well-being (when measured in terms of positive and negative affect), could fluctuate during early, mid and late transition. To address this issue, raw scores from the four predictor variables entered into the model(GHQ-30, PMT, PSQI, PAIS-T) were analysed in terms of the transitional stage (early, mid, late) of participants.

Single factor MANOVA, with transitional status as the independent variable, and scores on GHQ-30, PMT, PSQI, PAIS-T as the dependent variables, was used for this analysis. Results showed no significant main difference ($\underline{F}(65) = .443$, $\underline{P} = .893$) between participant scores on GHQ-30, PMT, PSQI, and PAIS-T when analysed in terms of transitional status (early, mid or late transition). Means, standard deviations and univariate statistics by transitional status are shown in Table 4.13.

Table 4.13: Descriptive and inferential statistics for psychogenic symptom severity (PSS) predictor variables by transitional status

Measure	Men. Status	N	Mean	SD	F-Value	p-value
GHQ-30	Early	41	35.22	12.90		
	Mid	7	35.14	11.32		
	Late	23	36.09	17.17	0.03	.971
PMT	Early	41	2.15	0.69		
	Mid	7	2.14	0.69		
	Late	23	1.91	0.73	0.85	.433
PSQI	Early	41	8.88	3.78		
	Mid	7	10.57	2.57		
	Late	23	9.43	4.60	0.59	.558
PAIS-T	Early	41	36.15	19.28		
	Mid	7	39.43	22.72		
	Late	23	38.70	20.64	0.16	.850

4.3.3 General Psychological Health (GHQ-30):

As can be seen from Table 4.12, the mean GHQ-30 scores for all participants, when categorised in terms of their transitional status, were under the 'best threshold' score of 39. When categorized in terms of good and poor psychological health, 46 participants had scores below the best threshold cut-off, but 25 had scores of 39 or more, indicative of poor psychological health. Independent t-tests again showed no significant difference between method of transition (natural/HRT-assisted) and GHQ-30 category membership (see Table 4.14).

Table 4.14: Descriptive and inferential statistics for GHQ-30 scores (natural and HRT-assisted participants) when classified as having good or poor psychological health

GHQ-30 Category	Method of Transition	No.	Mean	SD	t-value(df)	p-value
Good	Natural	35	27.29	6.09		
	HRT	11	26.82	6.01	-0.223 (44)	.825
Poor	Natural	15	49.60	10.87		
	HRT	10	52.60	13.13	0.622 (23)	.540

To establish whether there was any significant difference in terms of frequency of occurrence of participants with poor psychological health within the three stages of transition (early, mid, late) a Kruskal-Wallis K samples test was used. Results showed there were significantly more participants (regardless of natural or HRT-assisted transition) in the early transitional stage (n = 16, 39% of early group members), than in either the mid (n = 2, 29% of mid group members) or late transitional stage (n

= 7, 30% of late group members), with Chi-Square(2) = 23.00, p = .0001.

4.3.4 Predictive Value of Psychosocial Factors when Related to Nocturnal Thermoregulatory Symptoms:

Nocturnal hot flushes/sweats ranked as the second most *frequently* experienced symptom (Table 4.2) and the second most problematic in terms of *severity* of impact on maintenance of a normal lifestyle during transition (Table 4.3). In terms of major disruption, nocturnal hot flushes/ sweats ranked third, with 21% of participants attributing the maximum score of three to its impact on maintenance of normal lifestyle (Table 4.4). Nocturnal cold sweats ranked at 25 in terms of *frequency* and 23 in terms of *severity* of impact. The latter rankings would suggest nocturnal cold sweats are not seen as frequent or problematic for the greater majority of participants.

An independent t-test, with method of transition (natural or HRT-assisted) as the independent variable and total nocturnal thermoregulatory symptom severity (NTSS) as the dependent variable showed no statistically significant difference (p =>.05) between participants using natural transition (N=50, M=1.66, SD=1.49) and those using HRT (N=21, M=1.38, SD=1.20). Scores for both groups were therefore combined for predictive statistical analysis. A stepwise linear regression model with NTSS as the dependent variable and PSQI, GHQ-30, PAIS-T, MH and PMT

as the predictor variables was conducted. Table 4.15 shows the contribution to variance of the four predictor variables.

Table 4.15: Predictors of impact of nocturnal thermoregulatory symptoms (NTSS) on maintenance of a normal lifestyle during transition

Variable	R Square	R Square Change	F Change	Sig.F Change
PSQI	.119	.118	88.50	.000
PAIS-T	.144	.025	18.98	.000
GHQ-30	.174	.030	23.83	.000
PMH	.184	.009	7.41	.007

As can be seen from the above table, the main predictor variable was global sleep quality (PSQI), contributing 11.8% of variance. However, trouble sleeping was the most problematic HSC symptom in terms of both *frequency* of reported symptoms and *severity* of impact on maintenance of a normal lifestyle during transition. Because of this, it had been expected that global sleep quality (PSQI) would contribute more significantly to the predictive variance within this sub-cluster than the 11.8% reported. A subsequent examination of raw data from the 71 participants in this study showed that, in terms of *severity* of impact on maintenance of a normal lifestyle during transition:

- Twenty women recorded scores of three or greater (within a range of 0-6) for the combined *severity* of impact of nocturnal hot flushes/sweats (range 0–3) and nocturnal cold sweats (range 0–3).

- Twenty-one women recorded the maximum score of three (range 0-3) for the *severity* of trouble sleeping in terms of its impact on maintenance of a normal lifestyle.

However, of the 21 women who recorded the maximum score of three in relation the severity of impact of trouble sleeping on maintenance of a normal lifestyle, only 11 recorded a corresponding score of three or greater for the severity of impact of nocturnal thermo-regulatory symptoms. At face value, this result would suggest that in the case of half of the women who reported trouble sleeping as having a major disruptive effect on their normal lifestyle, this effect was not mediated by correspondingly severity scores in relation to nocturnal thermoregulatory symptoms. Also worthy of note, is the fact that the four psychosocial factors entered into the model (PSQI, PAIS-T, GHQ-30, PMT) accounted for only 18.4% of the total explained variance in terms of the severity of impact of nocturnal thermoregulatory symptoms on maintenance of a normal lifestyle during transition.

4.3.5 Summary of Results from Analysis B:

Psychogenic Symptoms:

- Four of the five psychogenic symptoms (trouble sleeping, lack of energy, sad/downhearted, difficulty in concentration) were featured in the top ten most *frequently* reported symptoms in the 33-item

HSC. The fifth symptom, nervous tension, was the eleventh most frequently reported symptom.

- All five psychogenic symptoms were ranked in the top ten symptoms in terms of the overall *severity* of impact on maintenance of a normal lifestyle during transition.

- In terms of major disruption (ie. maximum score of three), all five psychogenic symptoms were in the top ten most debilitating symptoms in terms of *severity* of impact on maintenance of a normal lifestyle. The highest ranked symptom was trouble sleeping, with 31% of participants according it the maximum score of three.

- There was no statistically significant difference between participant scores for those using natural transition and their HRT-assisted counterparts in terms of the *severity* of impact of psychogenic symptoms on maintenance of a normal lifestyle (PSS).

- Stepwise multiple regression showed general psychological health (assessed by GHQ-30) as contributing the greatest amount of predictor variance (40.2%) in terms of *severity* of impact of psychogenic symptoms on maintenance of a normal lifestyle during transition (PSS). Other variables entered into the model were pre-

menstrual tension (PMT) (9.3%), global sleep quality (PSQI) (5.4%), and psychosocial health (PAIS-T) (3.0%).

- Twenty-five participants (35%) displayed poor psychological health when assessed in terms of GHQ-30 'best threshold' cut-off of 39 and above. However, independent t-tests showed there was no significant difference between mean GHQ-30 scores of participants categorised as either having good or poor psychosocial health, when the independent variable in each case was method of transition (natural/HRT-assisted).

- In relation to the predictor variables that entered the model, a single factor MANOVA with transitional status (early, mid, late) as the independent variable, reported no significant main difference between participant scores on GHQ-30, PMT, PSQI and PAIS-T.

- Kruskal-Wallis K Samples test reported a significant difference in the frequency of participants assessed as having poor psychological health (GHQ-30 scores 39 and above) within transitional status (early, mid, late). The early transition group had significantly more participants with poor psychological health, than either the mid or late transitional groups.

Nocturnal Thermoregulatory Symptoms:

- Nocturnal hot flushes/sweats was the second most *frequently* reported symptom in the 33-item HSC, with 79% of participants recording at least one experience within the prior two-week period. In contrast, cold sweats at night were ranked at 25, with only 15.5% of participants experiencing this symptom.

- When ranking symptoms in terms of the *severity* of impact on maintenance of a normal lifestyle during transition, nocturnal hot flushes/sweats was the second highest ranked symptom in the 33-item HSC, with nocturnal cold sweats ranked at 23.

- Nocturnal hot flushes/sweats was ranked third in terms of major disruption, with 21% of participants recording a maximum score of three for *severity* of impact on maintenance of a normal lifestyle.

- An independent t-test found no statistically significant difference between participant scores for those using natural transition and their HRT-assisted counterparts in terms of the *severity* of impact of nocturnal thermoregulatory symptoms on maintenance of a normal lifestyle (NTSS).

- Stepwise multiple regression showed global sleep quality (PSQI) as the largest contributor to predictor variance in terms of *severity* of impact of nocturnal thermoregulatory symptoms (NTSS). However this variable only accounted for 11.8% of explained variance. While psychosocial health (PAIS-T), psychological health (GHQ-30) and effects of pre-menstrual tension on mood (PMT) were also entered into the model, their combined variance (including PSQI) only accounted for 18.4% of total explained variance in the model.

- Of the 21 women who recorded the maximum symptom *severity* score for the impact of trouble sleeping on maintenance of a normal lifestyle during transition, only 11 recorded a correspondingly high score for the *severity* of impact of nocturnal thermoregulatory symptoms on the maintenance of a normal life during transition.

CHAPTER 5

PINEAL MELATONIN

A Review of Literature

"…a meeting place between the Body and the Spirit…"

(Descartes (1596-1650) – a description of the function of the pineal gland)

5.1 Introduction:

As early as the 16th century, the scientist philosopher, Descartes recognised that the pineal gland played an important role in mental and physical health. Because of its location in the diencephalon, or the mid-brain, Descartes may well have been justified in his description of it as a "meeting place between the body and the spirit". Some 500 years later Cardinali (1981: 327) commented that, "[there is] probably no other organ in the body that has suffered so long from a lack of its true functional recognition as the pineal gland".

While our knowledge of the true function of the pineal gland is still in its infancy, this chapter describes some of the research into the role of melatonin, the principal hormone produced by the pineal gland.

Section 5.2 describes in simple terms the biosynthesis of melatonin. A wider presentation of the mechanisms of either melatonin production or

melatonin secretion is beyond the scope of this thesis. For a fuller description of melatonin biosynthesis, metabolism, and neural pathways the reader is referred to Cardinali (1981) and Reiter (1991).

5.2 Pineal Melatonin:

Melatonin is the principle hormone produced by the neuro-endocrinal pineal gland. Located in the diencephalon, and about the size of a pea, the pineal gland, as its name suggests, is shaped like a small pine cone (Raven & Johnson, 1992). In humans, the pineal gland was once thought to be the 'seat of the soul', or an archaic remnant of a parietal eye (Cardinali, 1981). However, in lower vertebrates (Arendt, 1988) and reptiles (Raven, & Johnson, 1992) it has often been referred to as the 'third eye', due to its structural similarity to the human retina and its ability to respond directly to light (Raven, & Johnson, 1992).

The role of the pineal gland in humans did not start to become apparent until the late 1950s. In 1958, Aaron Lerner, an American dermatologist, extracted a compound characterised as *N*-acetyl-5-methoxytryptamine from the pineal glands of many thousands of beef cattle (Arendt, 1988). Due to the compound's ability to cause pigment contraction in amphibian melanophores (eg. frogs), Lerner named this potent amphibian skin-lightening factor, melatonin (Arendt, 1988). Subsequent research established the human pineal gland as an actively functioning neuroendocrine organ. Its three main properties being that it:

- responded to both photic and hormonal receptor stimuli,
- exhibited circadian rhythms,
- was influenced by the metabolic activity of other endocrine glands (Cardinali, 1981).

Pineal melatonin is a derivative of the amino acid tryptophan (TRP), a secretion of the pineal gland. TRP is a precursor of serotonin (5HT), which is an intermediary product of the synthesis of melatonin (Zimmerman, et al. 1993). TRP is converted to 5-hydroxytryptophan through the action of tryptophan hydroxylase (TH), the rate-limiting enzyme in serotonin (5HT). Serotonin (5HT) is thought to attain its greatest concentrations in the pineal tissue due to the high TH activity within this gland (Cardinali, 1988). Pineal 5HT exhibits both cyclic and metabolic rhythms, with the highest levels occurring during light and the lowest during darkness, where the decrease in pineal concentrations levels of 5HT coincide with the rise in the nocturnal production of melatonin (Reiter, 1991). All aspects of melatonin synthesis pathways within the pineal gland are rhythmic, with pineal melatonin being secreted during the hours of darkness (Arendt, 1988).

Early research had suggested that, in humans, the major receptor, or binding site, for melatonin was located somewhere within the hypothalamic region of the brain (Cardinali, 1988). Although a very small organ (approximately 0.3% of the brain's weight), the hypothalamus plays

a major role in most aspects of behaviour, including sleep, temperature regulation, feeding, emotional and sexual behaviour, endocrine function and movement (Kolb & Whishaw, 1996). It consists of some 22 small nuclei, connecting fibres and the pituitary gland. The pars tuberalis (PT), located within the pituitary gland stalk, is the only common site containing melatonin receptors in all photoperiodic mammals (Weaver, Rivkees, Carlson & Reppert, 1991).

There is now substantial research evidence to show that the major regulator of melatonin secretion in humans is located within the hypothalamus. However, unlike photoperiodic mammals, its location is not in the pars tuberalis, but the supra-chiasmic nucleus (SCN) of the hypothalamus. Located in the anterior hypothalamus, dorsal to the optic chiasm, the SCN is recognised as the human body's major circadian pacemaker, controlling circadian (24 hour) cycles for numerous bodily functions, including the sleep/wake cycle (Ralph, Foster, Davis, & Menaker, 1990). Within higher-order mammals (eg. rhesus monkeys) both the SCN and the PT have been shown to be equal in their affinity as major receptors for melatonin (Weaver, Stehle, Stopa, & Reppert, 1993). In humans, however, specific melatonin binding areas have only been consistently detectable within the SCN (Weaver, et al., 1993). Research continues in animal studies to better understand the role of the SCN in the cyclical rhythmicity of melatonin. For example, a recent rat study by Bothorel, et al. (2002) had reported an approximate 100% increase in the

peak amplitude of the melatonin rhythm when exogenous melatonin (dosage rate 1 mg/kg) was injected either sub-cutaneously or directly into the SCN. This substantive increase in amplitude was not observed, however, when the melatonin was injected directly into the pineal gland.

5.3 The Function of Pineal Melatonin in Humans:

In a review article Arendt (1988) commented that, had Aaron Lerner sought funding in the late 1980s for a research project designed to isolate a compound from the pineal glands of many thousands of cattle, whose only function appeared to be as a blanching agent for frog skins, he would have had little chance of receiving any financial assistance. However, in the late 1950s Lerner did receive such funding, and as a result of his initial research project, the pineal gland has, in Arendt's words, "taken its place in mainstream biology and medicine" (1988: 205).

Because of Lerner's original research it is hardly surprising that much of the early research into the function of the pineal gland, and its primary hormone melatonin, was centred round animals, rather than humans. It is now well accepted that, in many species, pineal melatonin plays an essential role in photoperiodicity, where seasonal changes in daylight length affect animal coat growth, moulting, and in some cases, coat colour. However, the most obvious example of photoperiodicity is in the reproductive cycle of many animals, where control of mating

behaviour ensures that young are, more usually, born only at times when climates are most conducive to their survival (Arendt, 1988).

Studies showing the relationship between pineal melatonin and circannual rhythms in lower vertebrates eventually led to studies of its function in mammals. In a comprehensive review of pineal function in photoperiodic mammals, Reiter (1980) noted that research evidence was suggestive of melatonin being the indole responsible for mediating the effects of the pineal gland on reproduction. From previous research, melatonin had been shown to have both an antigonadotropic and a counter-antigonadotropic action. When exogenous melatonin was injected daily into Syrian hamsters late in the light phase of the light/dark cycle it caused gonadal collapse, similar to natural involution occurring at the beginning of the winter (dark) hibernation cycle. However, when deposited sub-cutaneously (therefore continually available) it prevented gonadal regression caused by exposure to darkness.

Unlike other mammals, humans are not photoperiodic. Humans exercise control over their own environment in terms of day length and temperature. Seasonal changes are artificially adjusted in many countries, when during Spring and Autumn one hour is added to, or taken away from, the 24 hour day/night cycle. Advances in technology have enabled artificial means to be employed to extend daylight hours, and to control interior environmental temperatures. Without the need for a

substantial increase in body hair to protect them during the colder months, nor a seasonal breeding pattern to protect their young from being born during inclement weather, the full role played by endogenous melatonin in humans is still under debate.

With initial mammalian research interest focussed around photoperiodicity, early research into the role of melatonin in humans centred on such areas as the sleep/wake cycle and the human reproductive system. In the mid to late 1970s technical and practical difficulties that lead to an inability to develop sufficiently sensitive and specific assay techniques to detect melatonin levels in humans were overcome (Miles, & Philbrick, 1988). Thus, during the last two decades there has been world-wide interest into the role played by melatonin in such diverse areas as circadian phase-shift disorders involved in jet-lag and shift work, to the inter-relationship of pineal function and metabolic activity within other endocrine gland systems. However, the remainder of this chapter outlines only research studies that relate to the involvement of melatonin secretion levels and/or rhythms in psychogenic and nocturnal thermoregulatory symptoms of menopausal transition.

5.3.1 Melatonin and Ovarian Function:

Nocturnal secretion levels of melatonin, and its primary metabolite, 6-sulphatoxymelatonin (6-STM) are highest in young children aged between one to three years (Waldhauser, & Steger, 1986). In a normal

prepubescent population, melatonin levels then gradually decline until puberty, when concentrations fall to a level that remains stable until late adulthood (Waldhauser, & Steger, 1986). It is argued that the decline in melatonin secretion levels between early childhood and adolescence in a normal population is due to an increase in the distribution volume of melatonin, as children grow taller and larger, without a commensurate increase in their secretion levels (Waldhauser, et al., 1988). An atypical decline in childhood to adolescent melatonin levels has been associated with precocious puberty, with research suggesting that children who exhibit precocious puberty have lower levels of melatonin than their non-precocious counterparts (Waldhauser, Boepple, Schemper, Mansfield, & Crowley, 1991). Conversely, successful treatment of delayed puberty has shown a rapid decrease in melatonin secretion levels to that of adult concentrations (Arendt, 1989).

In post-pubescent women, prior to commencement of menopausal transition, morning serum melatonin concentration levels significantly decrease throughout the luteal phase of the menstrual cycle (Fernandez, Malde, Montero, & Acuna, 1990). The late luteal phase of this cycle normally occurs at day 24 of the 28-day menstrual cycle, and is commonly associated with premenstrual tension. This has been established as a critical time for sleep disruption (Ito, et al., 1995, Driver, et al., 1996, Severino, & Moline, 1995), with more than 10% of women of reproductive age exhibiting changes in mood, sleep, eating habits and energy levels

(Steiner, 1992). In their review of previous studies, Parry and Newton (2001) report several areas of divergence in melatonin secretion levels and/or rhythms between normal cycling women and their counterparts diagnosed with premenstrual dysphoric disorder (PMDD). For example, when compared to a non-PMDD symptomatic control group, PMDD sufferers are reported as having earlier off-set times, a shorter duration and a decreased area under the curve of nocturnal melatonin secretions (Parry et al, 1990). In their luteal phase as compared to their follicle phase, PMDD-diagnosed women have delayed melatonin on-set time, their off-set time is advanced, and both the amplitude and mean levels of their melatonin secretion are decreased (Parry, et al., 1997(a).

During menopausal transition, levels of follicle stimulating hormone (FSH) and lutenising hormone (LH) are known to increase significantly, while progesterone and oestrogen levels decrease. While acknowledging the paucity of solid data with regard to specific changes in melatonin synthesis during the early perimenopausal period, Okatani, Morioka, and Wakatsuki (2000) have reported a temporary and transient increase in melatonin secretion levels in rats that may have resulted from decreasing levels of endogenous oestrogen.

However, increased levels of FSH are now acknowledged as the best predictor of the initial on-set of menopausal transition (Vakkuri, Kivela, Leppaluoto, Valtonen, & Kauppila, 1996). After examining five-

year age group cohorts from 35 to 75 years of age, Vakkuri, et al. noted that the sharpest decline in adult melatonin levels (41%, from 21.1± 2.2 pmol/h to 12.5± pmol/h) occurred in the cohort group 39 to 44 years of age. Levels then remain relatively stable until the middle 50s, when they again significantly decline (35% to 7.5 pmol/h). Vakkuri, et al. argue that the first decline is supportive of a permissive link between melatonin secretion and the initiation of menopause. They suggest that the second decrease in secretion levels is linked to increased aging, with a decreased level of activity by the pineal gland associated with this aging process (Waldhauser, et al, 1988).

More recent research by Zhou, Liu, Heerikhuzen, Hofman, and Swaab, (2003) appears to confirm these findings. Using a 24 hour saliva testing protocol, Zhou, et al. reported a lower amplitude of rhythm in the middle aged population (mean age 43 ± .04 years) when compared to their younger counterparts (mean age 22 ± .02 years). This lowering of amplitude continued to decrease with aging, where rhythms in old (66 ± 1.4 years) and oldest (83 ± 1.2 years) were significantly more variable than in either the young or middle-aged groups. Within their subject groups, the old and oldest groups had increased base-line (daytime) melatonin levels with slightly decreased on-set levels, but off-set levels more than two times higher than the oldest subjects in the other groups. Supporting the findings of Vakkuri et al. (1996) they also noted that their most striking finding was an strong initial decrease in circadian rhythms

within the middle aged group, with this group having only 60% of the nocturnal peak amplitude levels of their young age group counterparts.

5.3.2 Melatonin and the Sleep/Wake Cycle:

As previously noted in Section 5.3, initial mammalian research interest focussed on the role of melatonin in the sleep/wake cycle. To date there are over 40 published studies and several meta-reviews that explore the possible role of melatonin in the human sleep/wake cycle. Acknowledging that the exact nature of the role of melatonin in sleep architecture is still unclear, this section seeks only to provide a brief overview of such research.

Entrainment of the human sleep/wake cycle is via the retino-hypothalamic tract (RHT), a direct projection from the ganglion cells that start in the retina and terminate on the smaller dendrites of neurons within the SCN (Moore, & Lenn, 1972). Likewise, the cyclical rhythm of melatonin secretion appears to be synchronised through the retina's absorption of light and dark (Arendt, 1988). In her comprehensive review of melatonin research from 1958 to 1988, Arendt points to the strongly endogenous rhythm of melatonin, persisting in the absence of a light-dark cycle slightly out of phase with the commonly adopted 24 hour human sleep-wake cycle (Wever, 1986 cited in Arendt, 1988). Reviewing studies by Lynch, et al. (1978) and Lincoln, et al. (1985), Arendt suggests that melatonin is synchronised to 24 hours by the light-dark cycle, acting in

mammals via the retina and the retino-hypothalamic projection to the SCN. Acknowledging the work of Lewy, et al. (1980) and Reiter (1985) reporting light of a certain intensity and spectral conditions (known commonly in research as bright light) could suppress melatonin production at night time, Arendt concludes that light both entrains and suppresses melatonin production.

Melatonin secretion levels are at their lowest during the daylight hours, with secretion levels increasing as darkness approaches. In a normal adult population there is an observable steep rise in melatonin concentrations at about 10.00 pm, with average concentration levels showing a seven to eight-fold increase over normal daytime levels (Bispink, Zimmermann, Weise, & Leidenberger, 1990). Levels then appear to plateau somewhere between 2.00 am and 4.00 am (Moore-Ede, Sulzman, & Fuller, 1982, Bispink, et al., 1990). Exposure to artificial bright light immediately after the establishment of the peak nocturnal secretory plateau, has been shown to result in a dramatic (30%) drop in secretory levels. However, once darkness is restored, melatonin levels again return to their former plateau level (Bispink et al., 1990).

Changes in natural light during the year affect the amplitudinal rhythm of nocturnal secretion of melatonin (Bispink, et al., 1990), with exposure to extended natural light in the evening delaying the initial onset of nocturnal melatonin secretion, and darkness in the morning prolonging

plateau levels (Chase, & Gidal, 1997). Interestingly, while the amplitudinal rhythms of melatonin secretion are affected by changes in natural light, these changes do not appear to alter total secretory activity. For example, when separated by 8,000 miles and 24 degrees of latitude, healthy adults in Los Angeles had similar six-month mean values for overnight urinary melatonin concentrations as their counterparts in Stockholm (Wetterberg, et al., 1992).

The exact nature of melatonin's involvement in sleep regulation is still unclear. However, it would appear that phase shifts in human sleep can be affected by various manipulations, from administration of exogenous melatonin to working outside the normal daylight hours. Naturally occurring phase shifts have been observed in people whose working hours do not regularly coincide with the normal daylight working hours (ie. the typical 'nine to five' working day). Quera-Salva, Defrance, Claustrat, De Lattre, and Guilleminault (1996), reported that shift-workers on permanent day-shift exhibited a different melatonin acrophase (peak time of the fitted cosine) than those on permanent night-shift. The permanent day-shift workers were able to maintain a similar melatonin acrophase during days on and days off, whereas night-shift workers were unable to maintain a regular acrophase during days off, and had a delayed acrophase during days on (Quera-Salva, et al., 1996).

While exposure to bright light has been reported as a superior method of improving the circadian adaptation of shift workers, day-time administration of exogenous melatonin has also been shown to override the circadian system of shift workers for short periods, resulting in improvements in sleep patterns. Dawson, Encel, and Lushington (1995) compared adaptation to night shift in three groups of workers. The first group were exposed to bright light (4,000 - 7,000 lux) on a regular time schedule from midnight to 4.00 am on three successive night shifts. The second group were given low dose (4 mg in total) exogenous melatonin at 8.00 am, 11.00 am and 2.00 pm each day, prior to night shift work. The third (control) group received either dim red light treatment ($\leq$ 50 lux) or sucrose tablets identical to those containing exogenous melatonin. Using the control group to provide baseline data, Dawson et al., found that while phase shift, sleep quality and cognitive performance was most enhanced in the bright-light exposure group, the workers receiving exogenous melatonin also showed significant improvements in sleep quality. They noted that, while exogenous melatonin was unable to increase the degree of phase shift, its ability to affect a lowering of core body temperature could well have been responsible for enhanced sleep quality within this group of workers.

Deviant melatonin rhythms have also been found in women who complain of poor sleep quality during pregnancy. Although melatonin secretion levels increase during the third trimester of pregnancy, pregnant

women who report poor sleep during their last three months of pregnancy, have a marked difference in their nocturnal melatonin rhythms, with melatonin secretions tending to peak earlier than in either a normal population or good sleeping pregnant counterparts (Suzuki, et al. 1993).

In addition to its phasic relationship with the SCN, research has also pointed to the role of melatonin in nocturnal sleep propensity. Sleep propensity can be defined as the human body's peak time for falling asleep, where sleep to the first 30 seconds of stage two sleep, can be achieved within 1.5 minutes (Lavie, 1986). By using an ultra-short sleep-wake paradigm (where subjects were, during a 24 hour period, allowed 7 minutes sleep followed by 13 minutes awake) Lavie established two distinct features of sleep propensity. The first was an early evening nadir in sleepiness (described as the "forbidden zone for sleep") and the second in the late evening, where again there was a steep drop in sleep latency (the actual time taken to fall asleep). Lavie named this latter abrupt drop in nocturnal sleep latency as 'the nocturnal primary sleep gate'. As each participant in Lavie's study had his or her own 'nocturnal primary sleep gate', occurring at approximately the same time each night, he concluded that this sleep gate's stable individual characteristics underlined its role as a dominant feature of the entrained sleep/wake cycle in humans.

Tzischinsky, Shlitner, & Lavie, (1993) also employed the 24 hour ultrashort sleep/wake schedule to investigate the relationship between the nocturnal sleep gate and melatonin, as measured by the 2-hourly output of 6-sulphatoxymelatonin (6-STM). A strong correlation between the timing of the nocturnal sleep gate and the onset of nocturnal secretions of melatonin, prompted Tzischinsky, et al. to suggest melatonin was also involved in the onset of this nocturnal sleep propensity period.

Research has shown that nocturnal sleep duration and sleep quality declines with age. Although the acrophase of melatonin secretion has been reported as negatively correlated with age (Sharma, et al., 1989), not all older people complain of sleep problems. Nor is there evidence to suggest that diminishing total melatonin production levels is the primary cause of self-reported poor sleep in an aging population (Lushington, et al., 1998).

When comparing the relationship between sleep disorders and melatonin rhythms in an aging population (70+ years of age) with and without insomnia, and a young male control group (mean age = 24 years), Haimov, et al. (1994) reported a significant correlation between melatonin rhythms and poor sleep quality in the older participants. Those who complained of insomnia had significantly lower sleep efficiency and higher activity levels during sleep. Furthermore, they also had significantly different melatonin rhythms than their non-insomniac age-

matched counterparts, with melatonin secretion levels characterised by a lower peak (acrophase), delayed sleep onset, and delayed peak times.

However, total melatonin production levels do not appear to be directly implicated in differing sleep quality among older people. Lushington, et al. (1998) compared 24 hour urinary 6-STM secretion levels in a mixed-gender older population. The study population comprised 52 good sleepers (19 males, mean age = 65.3 years, 33 females, mean age = 63.5 years) and 56 sleep maintenance insomniacs (21 males, mean age = 66.2 years, 35 females, mean age = 64.3 years). The insomniac group self-reported significantly greater periods of wakefulness after initial sleep onset, less total sleep, lower sleep efficiency and poorer sleep quality than their good sleeping counterparts. However, there was no significant difference in either their total 24-hour 6-STM secretion means, or their 12-hour night-time secretion means. When adjusted for multiple comparisons there was also no significant relationship between measures of sleep and night-time melatonin secretion levels.

While also reporting no significant difference in 24-hour secretion levels of urinary melatonin (6-SMT), Kripke, Elliott, Youngerstedt and Smith (1998) did report deviant melatonin secretion rhythms in 42% of post-menopausal women who complained of poor sleep quality. Using data from 150 post-menopausal women (age range = 50 – 81 years, mean age = 71 years), Kripke, et al. reported that some poor sleeping

post-menopausal women had melatonin secretion timings 12 hours opposite the normal range. The majority of the 42% with deviant melatonin rhythms had acrophases that were either advanced (earlier than normal range) or delayed (later than normal range). Within this group, twice as many women exhibited advanced acrophases, resulting in waking earlier than planned, rather than trouble in falling asleep.

5.3.3 Melatonin and Nocturnal Thermoregulatory Symptoms:

As previously outlined in Chapter 2.4, one of the most commonly reported symptoms of menopausal transition is hot flushes and/or sweats. Believed to result from a disorder of temperature regulation within the medial pre-optic area of the hypothalamus (Woodward, & Freedman, 1994; Frishman, 1995), menopausal flushes cause a substantial increase in peripheral body temperature (Freedman, 1989).

While transitional women experience both diurnal and nocturnal flushing, nocturnal flushing has been reported as more problematic than diurnal flushing. Nocturnal flushing episodes leading to a reduction in the time spent in REM sleep have been implicated in significant impairment in transitional women's overall mental and physical health (Frishman, 1995).

In a review discussing the thermoregulatory physiology of transitional flushes, Kronenberg and Downey (1986) pointed to several

hypotheses put forward to explain nocturnal hot flushes. Among these were (i) apparent hyperthermia within the normal thermoregulatory system, leading to the activation of heat loss responses to return internal body temperature to homeostasis; (ii) direct activation of cutaneous blood vessels and sweat glands, where core body temperature (CBT) was normal, thus resulting in an initial lowering of CBT and the secondary activation of such effector mechanisms as shivering and vasoconstriction designed to return CBT to its previous level, or (iii) a transient lowering of the thermoregulatory set point within the hypothalamic area, triggering an autonomic response of vasodilation and sweating, designed to return CBT to its previous level. However, the relationship between menopausal hot flushes and gonadal hormones has also implicated the pituitary gland (Meldrum, Defazio, Erlick, Lu, et al., 1984). For example, gonadotrophin-releasing agonists, such as naloxone have been suggested as effective counters of the pulsatile release of lutenising hormone (Defazio, et al, 1983; Defazio, et al. 1984), in itself thought to be implicated in the aetiology of menopausal hot flushes (Frishman, 1995).

There is little doubt about the complementary role between core and peripheral body temperature in maintaining homeostasis. During the deconditioning of two Russian cosmonauts who spent 115 days aboard the Mir 18 space station, an excessive rise in core body temperature was attributed to decreased peripheral vasodilation (Greenleaf, 1997). This complementary role has also been supported by studies of core to

peripheral temperature exchange during hypothermic conditions. Under general anaesthesia, core hypothermia has been shown to result from an internal core to peripheral redistribution of body heat, where distal extremities accounted for 81% of heat loss from the trunk to the extremities (Matsukawa, Sessier, Christensen, Ozakie, & Schroeder, 1995). Similarly, induction of mild hypothermia in awake subjects has also shown core body temperature cooling to be directly associated with peripheral vasoconstriction and increased mean arterial blood pressure (Frank, et al., 1997).

Although research opinion is still somewhat divided on the effects of frequent nocturnal flushing episodes on sleep quality (Chapter 2.4), there is little doubt that core body temperature is implicated in sleep propensity and nocturnal thermoregulatory symptoms of menopausal transition. Like the sleep/wake pattern, human core body temperature (CBT) follows a strong circadian rhythm, where CBT is at its highest level during the day and its lowest level during the night (Zulley, Wever,& Aschoff, 1981). While the amplitude of the nocturnal decline in CBT is influenced by sleep (Barett, Lack, & Morris, 1993), the coincidence between the nocturnal peak sleep propensity period and the nocturnal lowering in CBT (Lack & Lushington, 1996), has suggested the CBT nadir as instrumental in initiating sleep onset. This role has been supported by research into Delayed Sleep Phase Syndrome (DSPS), a sleep-wake disorder, where sufferers have a chronic inability to fall asleep at the

desired clock time or to spontaneously wake in the morning at their desired time (Ozaki, Uchiyama, Shirakawa, & Okawa 1996). In DSPS, sufferers' sleep onset and offset times and their CBT nadir is significantly delayed when compared to their normal sleeping counterparts.

There is now substantial evidence to link melatonin secretion and the CTB nadir. The course and amplitude of nocturnal melatonin secretions, within a normal population, are temporally coupled to the initial decline in CBT, with some 40% of this decline being inversely related to increased nocturnal concentrations of melatonin (Cagnacci, Elliott, & Yen, 1992). Small doses of exogenous melatonin, administered to healthy young adults in the early evening have resulted in acute, although transient, suppression of CTB, with 5mg effecting a drop in CBT of 0.35 ± 0.02ºC. (Deacon & Arendt, 1995). Conversely, complete suppression of nocturnal melatonin secretion resulted in a similar (0.30º C) increase in normal nocturnal CBT (Cagnacci, Elliott, & Yen, 1992).

The mechanisms that mediate the action of melatonin on CBT are still unclear. However, in a normal adult population, melatonin appears to influence heat loss, and possibly heat production within the thermoregulatory centre of the hypothalamus (Cagnacci, Krauchi, Wirz-Justice, & Volpe, 1997). Through its involvement within the central thermoregulatory mechanisms of the hypothalamus, melatonin secretion levels and/or rhythms may also be implicated in nocturnal flushes

experienced by many women during their menopausal transition. As the pulsatile release of lutensing hormone has been implicated in menopausal flushes (Defazio, et al., 1983; Defazio, et al., 1994; Frishman, 1995), it is possible that, within a menopausal population, deviant melatonin secretions and/or rhythms may be implicated in nocturnal hot flushes and/or sweats. There is certainly evidence to show that during the luteal phase in normally menstruating women where there is a sharp increase in the level of LH within the blood stream (see Chapter 1.3.1), melatonin does not appear to exert its normal CBT lowering properties. This, it has been argued, could be indicative of a mechanism to promote higher body temperature, and thus better embryonic implantation and survival (Cagancci, et al., 1997). While not specifically examining the relationship between ovarian hormones and hot flushes, Bellipanni, Bianchi, Peirpaoli, Bulian and Ilyia (2001) also noted that in younger (43 – 49 years of age) peri-menopausal women, continuous low dose (3 mg nightly) exogenous melatonin resulted in a significant diminution of lutenising hormone to what they termed a more juvenile pattern of regulation.

5.3.4 Melatonin and Depressive Disorders:

The historical linking of the pineal gland to the seat of the soul, or the meeting place of the body and the spirit, led inevitably to the search for a link between pineal function and psychiatric disorders. As early as 1920, Becker used a 'stew' of animal pineal gland extracts in an attempt to treat schizophrenia. However, it was the structural similarity between *N*-

acetyl-5-methoxytryptamine isolated by Lerner (1958) and hallucinogen harmine that led to research suggestive of a link between the abnormal synthesis of melatonin and the occurrence of schizophrenia (Miles, & Philbrick, 1988). While any causal involvement of melatonin in the occurrence of schizophrenia remains unclear, sufferers of chronic schizophrenia are reported to display low melatonin secretion levels (Sharmir, et al., 2000).

Of more interest to this thesis, however, has been research into the role of melatonin in endogenous depressive disorders and in seasonal affective disorders. Many of the research studies outlined in this section are contradictory. The comments of various authors have been taken into account when explaining such contradictions. The studies cited show the continuing debate into the role of melatonin and depressive disorders

Initially, research into endogenous depression sought a link between low levels of nocturnal melatonin secretion and increased hypothalamic-pituitary-adrenal cortical (HPAC) axis activity. As hyperactivity within the HPAC axis had been reported in some 30% to 50% of those classified with endogenous depression, Low Melatonin Syndrome (LMS) was then proposed as the causal component of endogenous depression. For a comprehensive review of early research into LMS, the reader is referred to Miles and Philbrick (1988, 413-416).

Contrary to the LMS theory, Thompson, Franey, Arendt and Checkley (1988) reported a trend toward higher rather than lower melatonin levels in a small study of nine age and gender matched pairs of depressed and non-depressed participants. While their five female pairs were also matched on menopausal status (pre- and post-) it was not possible, given their sample size to speculate on the effect of menopausal status on study findings. Using more sensitive assay techniques and larger sample numbers Rubin, et al. (1992) also failed to confirm any significant relationship between the HPAC and low nocturnal secretion of melatonin. In a comparative study of 38 mixed gender participants diagnosed with endogenous depression, and their 38 gender and age matched non-depressed counterparts, Rubin et al. also reported a trend toward higher rather than lower nocturnal concentrations of serum melatonin in the depressed group. However, they noted that this trend was primarily accounted for by 14 pre-menopausal participants. When excluded from analysis, male and female depressed participants did not differ significantly from their non-depressed counterparts.

More recently Kripke, et al. (2003) queried whether low melatonin secretion levels in those suffering from depression were more related to ageing than the depression *per se.* They postulated that melatonin abnormalities frequently associated with affective disorders might interact with age-related changes in melatonin levels and/or rhythms (previously noted in Chapter 5.3.1 of this thesis). Of their 72 mixed gender

participants 55% had a lifetime history of affective disorders, with the remaining 45% previously or currently experiencing single or intermittent depressive episodes. Kripke et al. reported significantly greater melatonin secretion levels (both in home and laboratory trials) within their 'lifetime' depressive group. However, they qualified this result in terms of the effects of multiple comparisons. When they applied Bonferroni adjustments, their results showed no significant relationship between mood and melatonin parameters, regardless of the affective (lifetime or intermittent) status of participants.

In their discussion, Kripke et al. (2003) noted that their results were not consistent with those of Tuunainen et al. (2002). The study by Tuunainen et al. into the effects of depression and endogenous melatonin in 382 post-menopausal women was carried out simultaneously and within the same laboratory complex as that of Kripke et al. Tuunainen et al. reported a significant relationship between a history of depression and a longer duration of melatonin (6-SMT) secretions, with a later off-set marginally related to current severe depression and a later acrophase to lifetime depression.

This again highlights the problems in interpreting differing research results with regard to the role of melatonin. In this instance, Kripke et al. suggest reasons for the inconsistencies could be related to use of beta-blockers, gender of participants and type of study environment. In the

Tuunainen et al. study several women were not excluded on the basis of their use of beta-blocking medication, although beta-blockers have been shown to suppress melatonin. The Tuunainen et al. study, while larger in number than the Kripke et al. study was made up of women (mean age 67.5 years) and was conducted exclusively in their home environment. In comparison Kripke et al. participants, while having a similar mean age (68 years) comprised 49 women and 23 men, with melatonin samples collected in both the home and the laboratory environments.

Apart from the possible effects of alterations in actual melatonin secretion levels, other researchers have argued the role of alterations in the circadian rhythms of plasma pituitary and pineal hormones (prolactin, thyrotrophin and melatonin) as having a relationship to depression in some people. It has been suggested that these circadian disturbances may be related to the desynchronisation of the circadian rhythms of central catecholamine and/or serotonin activity common in bi-polar illnesses (Mendlewicz, et al., 1983). Referred to as the internal coincidence model, this theory argues that harmonious synchronisation of circadian rhythms depends upon the dual influence of both internal clocks and external temporal information. Thus the phase advancing of the strong oscillator in reference to the weak oscillator causes depression, where the internal clocks of depressed subjects are blind to the environmental time cues leading to internal desynchronisation (Souetre, Pinquey, Salvati & Robert, 1985). This theory has received more recent

support with research reporting improved sleep in bipolar sufferers being linked to the phase delaying effects of on-going lithium treatment on biological rhythms leading to better synchronization of the sleep-wake cycle (Benedetti, et al. 2001).

Because of its involvement with circadian entrainment of the light/dark cycle, melatonin has also been implicated in seasonal affective disorders (SADs). SADs are characterised by seasonally recurring episodes of depression during Autumn and Winter, with remissions occurring during Spring and Summer (Waldhauser, et al., 1993). In a brief review of SADs, Waldhauser, et al. pointed to an early single-subject study by Lewy et al. (1982) in which a patient with SAD showed remission after prolonged bright light treatment. The Lewy et al. study led other researchers to explore the role of melatonin in SADs. In a review article entitled 'Toward understanding the mechanism of the action of light in seasonal affective disorder', Rosenthal and Wehr (1992) referred back to their earlier studies that sought to clarify the role of melatonin in seasonal affective disorders. With participant groups of SAD sufferers they first used bright light therapy and exogenous melatonin in an attempt to reverse the anti-depressant effects of bright light (Rosenthal et al., 1986, cited in Rosenthal & Wehr, 1992). While this protocol resulted in the reintroduction of some symptoms, the general level of depression did not increase after withdrawal of light therapy and the introduction of exogenous melatonin. Similarly, the use of beta-adrenergic blockers

(known to reduce melatonin secretion levels) resulted in no significant improvement in depressive symptoms in SAD participants given the beta-blockers and others given a placebo (Rosenthal et al., 1988, cited in Rosenthal & Wehr, 1992). At this time, they concluded that melatonin secretion did not play a critical role in the pathogenesis of SAD.

In more recent research Wehr, et al. (2001) measured the 24 hour melatonin secretion levels obtained in constant dim light conditions during winter and summer of 55 SAD sufferers and their 55 matched non-symptomatic counterparts. Their results indicated that within the SAD group, the nocturnal period of melatonin secretion was significantly longer in winter than in summer ($p = .001$) with winter secretion periods 9.0 ± 1.3 hours and summer secretion 8.4 ± 1.3 hours. Their non-SAD matched counterparts no such significant change between winter and summer ($p = .500$).

While bright light treatment is now recognised as an effective treatment for SADs, research opinion is still unclear as to the role of melatonin secretion levels and/or rhythms in this treatment. Both Rice, Mayor, Tucker, and Bielski (1995) and Partonen, Vakkuri, and Longqvist (1997) failed to find any evidence of a significant relationship between melatonin secretion levels and/or rhythms and clinical remission in SADs. Rice, et al. noted that treatment with both full spectrum and cool white light did result in significant increased in mean melatonin concentrations,

with a significant rise at optimum on-set time (20:00 and 22:00 hours). While treated participants recorded improved scores on psychometric measures of depression, melatonin phase advance was viewed as insufficient to induce clinical remission (a 50% improvement in scores) in all participants. However, they did note the possibility that the non-responders (ie. participants with less than 50% improvement in scores) may have had what they termed as "a varient of seasonal depression that does not respond to light therapy" (p.226).

Wirz-Justice, et al. (1996) investigated the use of natural light as a treatment for SADs. Their study compared SAD sufferers who were exposed to regular amounts of natural light (a one-hour early morning walk outdoors) with sufferers exposed to placebo level low-dose (0.5 hr @ 2,800 lux) artificial light. After one week of natural light treatment, clinical remission (a 50% improvement in scores on the Hamilton Depression Index) was reported in sufferers treated with natural light, which was maintained during one week's withdrawal of treatment. No such remission was noted in the placebo group. Wirz-Justice, et al. also reported a change in melatonin rhythms within the natural light group with 12 of the 17 participants showing a phase-advance at on-set and three showing a phase-delay. No significant modification of on-set was found in their placebo level artificial light group counterparts.

As can be seen from the above-mentioned studies, research opinion is still divided in terms of the role of melatonin in areas that impinge on psychogenic and nocturnal thermoregulatory symptoms of menopausal transition. There are contradictions in terms of overall secretion levels and in terms of on-set, off-set, and acrophase rhythms.

CHAPTER 6

STUDY 2

THE ROLE OF MELATONIN IN THE PSYCHOGENIC SYMPTOMS OF MENOPAUSAL TRANSITION

Aims and Methodology

"I would wake up as Doctor Jekyll and go to bed as Mr Hyde – and in between I would change my personality several times" (A participant's view of the effects of her psychogenic symptoms during menopausal transition)

6.1 Rationale and Aims:

As outlined in Chapter 5, research has shown that melatonin is implicated in the on-set of puberty, in the phasing of the menstrual cycle, in changes within this cycle during pregnancy, in overall quality of sleep, in the relationship between core body temperature and sleep on-set and maintenance, and in some depressive disorders. Melatonin secretion levels have also been implicated in the commencement of menopausal transition. One of the few studies to explore the relationship between ovarian hormones and melatonin in both a pre-menopausal, peri- and menopausal population (Fernandez et al., 1990) reported morning levels of serum melatonin decreased with age, reaching their then lowest levels in menopause. They also reported a significant negative correlation between melatonin and FSH, which was supported by a later study (Vakkuri, et al.,

1996), that suggested the increase in FSH was the best predictor of the on-set of menopausal transition. Somewhat surprisingly, little research has looked at the role of melatonin in a dedicated menopausal population. For example, in his review of literature into the potential use of melatonin replacement therapy for post-menopausal women, Brzezinski (1998) pointed to the lack of research within a transitional population, where "no data exist on the possible contribution of altered melatonin secretion to menopause-associated insomnia" (p 62).

There is little doubt that the most frequent and problematic symptoms of menopausal transition are those associated with the cluster of psychogenic symptoms (defined in this research study as: trouble sleeping, feelings of sadness/downheartedness, nervous tension, difficulty in concentration and lack of energy), and thermoregulatory disorders that result in diurnal and nocturnal flushes and/or sweats. In line with similar studies, results from Study 1 have shown trouble sleeping as the most frequently reported symptom (79% of participants). It was also the most debilitating in terms of severity of symptom impact in maintenance of a normal lifestyle during transition, with 31% of participants recording the maximum score for impact on their normal lifestyle. Nocturnal hot flushes/sweats featured as the second most frequently reported symptom (70% of participants) with 21% of participants also reporting maximum scores in terms of its disruptive impact. All other psychogenic symptoms

featured in the top ten when ranked in terms of major disruptive symptoms in Study 1.

While Study 1 assessed the severity of impact of menopausal symptoms, and the predictive value of psychosocial factors on maintenance of a normal lifestyle during transition, Study 2 sought to explore the role of melatonin in the incidence of psychogenic symptoms. It is acknowledged that establishing a direct link between melatonin secretions and/or rhythms would require extensive study. This naturalistic pilot study seeks to explore whether mild psychogenic symptoms, including problems with sleep, could be associated with some dysregulation of melatonin secretion levels and/or deviance in melatonin rhythms. Similarly, the role of melatonin cannot be ignored when looking for a central phenomenon to explain nocturnal hot flushes/sweats in women experiencing menopausal transition. In this latter context, the initial design for Study 2 had envisaged concurrent monitoring of peripheral body temperature (PBT) and exposure to natural light during the melatonin sampling period. However, this proved impracticable due the design of the PBT probe recommended for use with physiological data monitoring devices (PDMD) available to this study. In view of the body of research linking the light/dark cycle to the entrainment of melatonin rhythms (see Chapter 5.3) a decision was therefore made to monitor exposure to natural light during the melatonin sampling period. While nocturnal thermoregulatory symptoms are not classified within the

psychogenic symptom cluster, they have been implicated in sleep quality during menopausal transition (see Chapter 2.4). Thus, Study 2 also sought to explore the relationship between nocturnal peripheral body temperature and sleep quality in participants assessed as having good and poor psychogenic health (see Section 6.2.2 and 6.2.3).

6.2 Selection Criteria & Study Procedure:

6.2.1 Selection Criteria:

Of the 71 participants in Study 1 (The Impact of Menopausal Symptoms on Lifestyle during Menopausal Transition), 17 women indicated they did not wish to be contacted with regard to Study 2. Of the 54 remaining women, 10 were unable to be contacted at the time of commencement of Study 2, leaving a potential study pool of 44 women.

As several months had elapsed between Study 1 and Study 2, each of the 44 potential participants was asked to again complete the Health Symptom Checklist (HSC). Using participants' *latter* psychogenic frequency symptom (PSF) scores as indicative of women with high and low psychogenic symptom frequency (PSF scores), 13 women with the highest PSF scores and 13 women with the lowest PSF scores were invited to participate in Study 2. Participants with high scores on psychogenic symptom frequency were classified as having poor psychogenic health, while women with low PSF scores were classified as having good psychogenic health.

Study 2 sought to investigate the role of melatonin in the five psychogenic symptoms of menopausal transition. Some research studies into the involvement of oestrogen in brain chemistry have linked oestrogen to tryptophan regulation and to the metabolism and transportation of serotonin (cited in the review by Sherwin, 1996). As outlined in Chapter 5.2, melatonin is a derivative of tryptophan, which in itself is a precursor of serotonin, an intermediary product of the synthesis of melatonin. Thus, in designing the selection protocol for Study 2 there was a concern that HRT usage may confound the study outcomes. In effect, should HRT-assisted participants be excluded from the sub-set of Study 1 participants selected for Study 2?

Results from research into the relationship between oestrogen-based HRT treatments and melatonin secretion levels are contradictory at the present time. For example, when investigating the effects of exogenous melatonin and hormone replacement therapy on vascular reactivity and blood pressure in a post-menopausal population, Cagnacci, et al. (2000) reported no significant differences in either baseline melatonin secretion levels or levels after administration of exogenous melatonin between women undergoing natural transition and those using HRT. Their results supported the previous findings of Brzezinski, et al. (1994) who also reported no alteration in melatonin secretion levels in women undergoing IVF treatments, even though these women were

subjected to substantially increased levels of exogenous estradiol to promote ovarian stimulation.

Contrary to the above mentioned results, Bartsch, Seeger, Muck and Lippert (1995) reported inconsistent findings when examining the effects of both transdermal and oral estradiol treatments within a group of mid-stage transitional women exhibiting climacteric complaints. Bartsch, et al. failed to find any statistically significant main effect in relation to melatonin secretion levels and the type of estradiol delivery. However, an investigation of the individual profiles of participants showed either stimulation or inhibition of secretion levels in response to exogenous estradiol. These individual responses did not differ between the transdermal and oral treatment groups.

One research study that did report a statistically significant decrease in melatonin secretion levels after oestrogen treatment was that of Okatani, Morioka, and Wakatsuki (2000). During their eight week trial using Premarin, they reported significantly lower serum melatonin concentrations than concentration levels prior to treatment. Okatani, et al. cautioned against any specific conclusions being reached with regard to the effects of exogenous oestrogen on melatonin secretion levels. In their opinion the inconsistency of research results in this area could be due to differences in the type, dosage rates, and duration periods of oestrogen treatments.

It could be argued that because of such inconsistent results, women using HRT should be excluded from the second stage of the present study. However, within this group of participants, results from Study 1 found no significant differences in terms of overall perception of severity of impact of menopausal symptoms, psychosocial health, or psychogenic symptom frequency between participants undertaking natural transition and those undertaking HRT-assisted transition. Based on the similarity of their results, especially in relation to the incidence of psychogenic symptoms, it was decided to include women from Study 1, providing they met the psychogenic symptom selection criteria for Study 2.

As several months had elapsed since Study 1, the participants' current PSF scores were again compared in terms of transitional status (natural/HRT-assisted). An independent t-test showed no significant difference between participants terms of transitional status and PSF scores, with $\underline{t}(20)=-.132$, $\underline{p} =>.05$ (see Table 6.1 for means and standard deviations). Although selected on the basis of PSF scores, nocturnal thermoregulatory frequency scores (NTFS) were also compared between transitional status groups. Again, an independent t-test showed no significant difference between the two transition groups, with $\underline{t}(20)= .440$, $\underline{p} =>.05$ (see Table 6.1)

Table 6.1 Means and standard deviations by transitional group used in Study 2 selection criteria

Method of Transition	Subset	No.	Mean	SD
Natural	PSF	13	18.77	21.50
HRT-Assisted	PSF	9	19.89	16.41
Natural	NTSF	13	7.54	6.99
HRT-Assisted	NTSF	9	6.00	9.47

6.2.2 Study Protocol:

Telephone discussions were held with each of the 26 participants to arrange a suitable week for their study participation. At that time they were given an outline of the requirements of Study 2. They were again informed that the study had the approval of the Human Ethics Committee of Victoria University, Melbourne, and that, as this was a voluntary study, they had the right to withdraw at any time during the study. To ensure confidentiality, each participant retained their initial (Study 1) code number, which was used as an identifier on all melatonin saliva samples, and questionnaire booklets.

Full details of the instructions for Study 2 are included as Appendix 6.1. The following is a brief description of the study protocol. Details of saliva sampling techniques and physiological monitoring can be found in Section 6.3 – Measures Used.

Saliva Samples:

- Saliva sampling was undertaken from late April to mid September, during the Australian non-daylight saving period (late March to late October).

- Saliva sampling commenced at 9.00 am and continued on a 3-hourly basis up and including 6.00 pm to establish a daytime baseline level.

- From 8.00 pm onward saliva sampling continued on an hourly basis up to and including a midnight sample.

- Participants who woke during the night for any extended period took additional samples at their times of awakening.

- Each participant took a "first awakening" morning sample, and a final sample at 10.00 am on Sunday morning.

Physiological Monitoring:

- From first awakening on Saturday morning until midnight Saturday, participants wore a light monitor to assess their exposure to natural light during the saliva sampling period.

- For the five sleep nights of the study period, commencing midnight Saturday, participants wore:
  - a wrist actigraph to monitor nocturnal activity during sleep,
  - a peripheral body temperature probe on the dorsal surface of their predominant middle finger to monitor peripheral body temperature.

Sleep Quality Logs:

- During the study period, participants completed sleep logs to record their subjective sleep quality (normality, efficiency and fragmentation), incidence of mid-sleep awakenings, and incidence and severity of night hot flushes/sweats (see Appendix 6.1).

6.3 Measures Used:

6.3.1 Melatonin Collection and Measurement:

Melatonin concentration levels can be obtained from plasma, saliva and urine. There is little doubt that the most accurate measure, in terms of concentration levels, is that obtained from blood plasma. However, this method involves plasma collection via an intravenous catheter, or the insertion and monitoring of IV cannulas by a trained nurse or similar health professional. Measurement via urine is far less invasive, but does require a degree of disruption to normal routine, both in terms of

collection and storage of urine samples. The advantage of collection by saliva is that it allows study participants to maintain their normal daily routine, with only minimum disruption in terms of ingestion of food, drink or nicotine for a 20 minute period prior to sample collection.

There are differences in concentration levels of melatonin when obtained from samples of plasma and saliva. Using plasma concentrations, the evening on-set level for serum melatonin has been marked as the first interpolated point above 10 pg/ml that continues to rise (Lewy et al., 1992) with the equivalent point for salivary melatonin shown as 3 pg/ml. Melatonin rhythms, in terms of evening on-set and acrophase for both serum and saliva, have been reported as significantly correlated, and following the same profile. For example, within a non-clinical population, reported plasma (serum) concentration levels of melatonin, while significantly higher than those obtained from concomitant saliva samples follow the same profile for evening on-set and acrophase (Laakso, Porkka-Heikanen, Alila, Stenberg, & Johansson, 1990). Using a clinical population (rapid on-set bipolar disorder) a similar profile pattern was reported by Leibenluft, Feldman-Naim, Turner, Schwartz and Wehr (1996) in terms of the relationship between plasma and saliva sampling, where an interclass correlation of 0.93 was reported when concomitant sampling of plasma and saliva were analysed.

Saliva can be collected by having participants directly expel approximately 5cc of saliva into a sterile test tube. More recently, salivettes have replaced the direct expel method. Salivettes are small sterile tubes that contain a material-based insert. The insert is chewed gently and retained in the mouth for three to five minutes. It is then expelled into the sterile tube of the salivette, and sealed prior to being frozen. Inserts come in a variety of materials. This study used salivettes containing an unprepared polyester insert (supplied by Sarstedt Australia Pty Ltd) rather than salivettes containing a cotton insert, as these were thought to have better storage properties (personal conversation with Emma Gould, melatonin researcher, La Trobe University, Melbourne).

After enquiries into both private laboratories and tertiary institutions, La Trobe University School of Psychological Sciences was chosen to undertake melatonin RIA testing. From their prior experience in this area, they recommended the Buhlmann melatonin radio-immunoassay kit (RK-DSM2) as the most suitable to fit this study's profile in relation to direct saliva testing. The Buhlmann kit reports a minimum detectable concentration level at 0.2 pg/ml. Values from reported mean intra-assay precision within run (obtained from 20 pairs of values from each saliva sample in a single run)and inter-assay (run-to-run) are shown below:

Table 6.2: Intra-assay/ inter-assay precision (within run/run-to-run):

Sample	Mean	SD	CV%
Intra-assay			
Daytime	0.57	0.061	10.8
Evening	3.56	0.145	4.1
Night time	24.42	1.169	4.8
Early Morning	7.24	0.188	2.6
Inter-assay			
Daytime	0.82	0.136	16.5
Evening	3.38	0.300	8.9
Night time	25.41	2.121	8.3
Early Morning	8.95	0.583	6.5

Reproduced from Buhlmann's RIA Kit information booklet – page 9

Due to the high cost of radio-immunoassay testing (RIA), this study used a shortened testing schedule. Samples were take three hourly from 9.00 am to 6.00 pm on a Saturday, to establish a daytime base-line level. From 8.00 pm onward, up to and including midnight, samples were taken hourly to establish evening on-set levels. Participants who woke during the night, and believed they would not return to sleep within a few minutes were asked to take additional samples and note the time of sampling. To ensure that their melatonin levels were not affected by artificial light, a dim light torch was provided for this. All participants were required to take a 'first-awakening' sample at the time on Sunday morning when they believed they would not be able to return to sleep, and to take a further sample at 10.00 am on Sunday.

6.3.2 Physiological Monitoring:

During the last two decades, advances in technology led to the miniaturisation of physiological data monitoring devices (PDMD). Initially these devices were used to monitor nocturnal activity levels during sleep, and were often referred to as 'actigraphs'. As they could be used in the home environment, they were seen to provide a more ecologically valid pattern of typical nocturnal activity than that provided in the artificial surroundings required by polysomnography (Cole, Kripke, Gruen, Mullaney, & Gillin, 1992).

PDMDs are now commonly used to simultaneously monitor a number of physiological functions. These can include such functions as core and peripheral body temperature (rectal, oesophageal, skin and ear canal), heart rate (including inter-beat intervals), diurnal and nocturnal activity levels. Data is sampled and aggregated at a constant time interval, or epoch. Epoch- by-epoch samples are then stored in the miniaturised device and downloaded into a computer at the end of the sampling period, for further analysis.

This study used the Mini Logger Series 2000, supplied by Mini Mitter Co. Inc. USA to provide nocturnal activity measurement, peripheral body temperature measurement, and exposure to natural light. The constant sampling interval (epoch) was set at 16 seconds for all the above measurements.

The following sections (6.3.2.1 to 6.2.3.3) briefly outline the rationale for each of the three physiological measures used in this study.

6.3.2.1 Nocturnal Activity Monitoring:

Nocturnal activity was monitored using a band, worn on the dominant wrist, and connected to a miniature acceleration sensor that translated physical movement into a numeric representation. While activity levels can be monitored via the wrist or ankle, research has shown that during sleep, nocturnal activity decreases in the order of wrist, ankle and trunk (Middelkoop, van-Dam, Smilde-van-der-Doel, & van-Dijk, 1997), with dominant wrist monitoring giving the optimum activity level. Based on this, study participants who were right-handed, were instructed to wear the band around their right wrist, and those who were left-handed, to wear it around their left wrist.

Stored data was converted using an in-house software algorithm (NUVUT) to give Mean Activity Level (MAL), Movement Index (MI), Mean Immobility Period (MIP) and Fragmentation Index (FI). This algorithm was previously used in the author's Honours thesis (Bliss, 1998), to establish congruence between subjective and objective sleep patterns within a group of peri-menopausal women. For more information on the validity of the activity variables, the reader is referred to Middelkoop, van Hilten, Kramer, and Kamphuisen (1993) and van Hilten, Braat, van der Velde,

Middelkoop, Kerkhof, and Kamphuisen (1993). Briefly, these variables are defined as:

- **Mean Activity Level (MAL)**: The mean activity count per 16 second epoch within a given time period.

- **Movement Index (MI)**: The percentage of epochs with an activity count greater than zero as a proportion of all epochs within a given time period.

- **Mean Immobility Period (MIP)**: The mean duration, in minutes, of uninterrupted immobility (where activity = 0), within a given time period.

- **Fragmentation Index (FI)**: The number of immobility periods of short duration (one to four successive 16 second epochs) as a percentage of the total number of immobility periods of all durations.

6.3.2.2 Peripheral Body Temperature Monitoring:

Peripheral body temperature (PBT) in humans can be measured at a variety of sites on the outer skin. This study chose to measure PBT via the dorsum of the dominant hand middle finger, using a YSI 400 series thermistor. The dorsum of the right hand middle finger had previously

been used as a measurement site for the assessment of hot flushes within a menopausal population (Freedman, 1989). No research evidence was found to suggest that PBT measured from the right hand middle finger differed from that obtained from the left hand middle finger. However, as previously mentioned, there was evidence to show a difference in nocturnal activity levels between the dominant and non-dominant wrist. In this study, both the PBT skin probe and the nocturnal activity wrist band needed to be worn concurrently during sleep, and connected via conduction wires to the miniaturised monitoring device. It was not considered practicable to have participants who were left handed, wear the wrist band on their left wrist and the skin probe on their right middle finger. Thus, all study participants were instructed to place the skin probe on the dorsum of their dominant hand middle finger, to correspond with the placement of the wrist-band.

A software program (TEMPVU) was designed to convert the PBT epoch representations into usable statistical data. For this study, TEMPVU was used to aggregated epoch samples into the following analytical variables:

- **Minimum Mean Temperature (MiMT):** The minimum mean nocturnal peripheral body temperature over the study period.

- **Maximum mean temperature (MaMT):** The maximum mean nocturnal peripheral body temperature over the study period.

- **Hours At Temperature (Hours):** Number of hours at each temperature range, where a 1°C incremental range was calculated from 29°C up to and including 38°C.

6.3.2.3 Light Monitoring:

Previous research has established a causal link between daylight/ darkness and the cyclical rhythms of melatonin secretion in humans (see Chapter 5). It was therefore of interest to this research study to assess the level of exposure to light by study participants at the time of collection of saliva samples.

This was achieved by having study participants wear a light sensor from 9.00 am to midnight on the day of saliva collection. The sensor was a cadmium sulfide photoresistor-based sensor with a lux range of approximately 10 to 10,000 lux. Accuracy was quoted at typically ± 5-15% over the lux range, and the device was calibrated to an NTS traceable light standard. Again an in-house software program (LUXVU) was used to convert data for further analysis. This program had previously been used in conjunction with the light sensor to assess the role of light as a critical determinant of nocturnal sleep quality in a healthy aged population (Hood, Bruck, & Kennedy, 2002). Epoch samples were aggregated into total exposure time at 500, 3,000 and 10,000 lux. The program also allowed a breakdown of time exposed at each of the three lux points at hourly increments.

CHAPTER 7

RESULTS OF STUDY 2

7.1 Participants:

The selection criteria for participation in Study 2 was based on five psychogenic symptom frequency scores (PSF), assessed over a prior two-week period. The possible score range was 0 to 70, where a score of 0 equated to no experience of any psychogenic symptoms over the previous two-week period, and a score of 70 equated to experience of all five symptoms for each of the previous 14 days. The psychogenic symptoms used were trouble sleeping, feeling sad/downhearted, nervous tension, difficulty in concentration and lack of energy.

Initially 13 women with the lowest PSF scores and 13 women with the highest PSF scores agreed to take part in Study 2. Subsequently, one woman within the low PSF score group and two women within the high PSF group elected to withdraw from the study. The remaining 12 women with the lowest PSF scores (range 0–10, mean = 5.00, SD = 3.81) were designated as having good psychogenic health and 10 women with the highest PSF scores (range 19–66, mean = 36.30, SD = 15.64) were designated as having poor psychogenic health.

Of the 12 participants assessed as having good psychogenic health, 8 were undergoing natural transition, while 4 were undergoing HRT-

assisted transition. Within the poor psychogenic health group, 5 women were undergoing natural transition and 5 were using HRT. The overall mean age of the 22 participants was 50.00 years (SD = 3.77 years, range = 44.67 – 58.41 years).

Independent t-tests were used to establish whether there was any statistically significant difference between each of the two groups (good/ poor psychogenic health) based on age, transitional status, or assessed PSF status. As shown in Table 7.1 there was no significant difference in age of participants with regard to either their choice of transition or their allocated PSF status. As expected, there was a significant difference (p = .0001) between the PSF scores of women assigned to the good psychogenic health group and women assigned to the poor psychogenic health group.

Due to equipment problems, not all participant results were obtained for each of the four testing criteria (melatonin, lux, peripheral body temperature, sleep activity levels). The number of participants whose results were included have been shown at the beginning of each of the follow sections. The implications of equipment problems in terms of the validity of these results are discussed in Chapter 8.

Table 7.1: Descriptive and inferential statistics for Study 2 participants

AGE & CHOICE OF TRANSITION:

Choice of Transition	No.	Mean Age	Std Dev	t-value(df)	p-value
Natural	13	48.86 yrs	3.60 yrs		
HRT-Assisted	9	50.18 yrs	4.23 yrs	-189(20)	0.852

AGE & ASSIGNED PSF STATUS:

Status	No.	Mean Age	Std Dev	t-value(df)	p-value
Good	12	49.24 yrs	3.75 yrs		
Poor	10	50.89 yrs	3.79 yrs	-1.026(20)	0.317

PSF SCORES:

Status	No.	Mean Score	Std Dev	t-value(df)	p-value
Good	12	5.00	3.81		
Poor	10	36.30	15.64	-6.727(20)	0.0001

7.2 Melatonin Secretion Levels and On-set of Rhythm:

As mentioned in Chapter 6.4.1, the cost of RIA testing prohibited 24 hour on-set and off-set of melatonin rhythms being established for this study sample. In terms of melatonin rhythms, the results shown below relate only to on-set of rhythm. Similarly, average secretion patterns do not take into account any variations occurring between midnight and first full morning awakening. The study criteria did provide for mid-sleep awakening sampling, and of the 22 participants in Study 2 only eight women provided testable mid-sleep samples. Of these eight women, four were classified within the good psychogenic health group, and four were classified within the poor psychogenic health group. Thus, for the purpose of analysing overall secretion levels, the levels obtained for mid-sleep

awakening were excluded. Time values obtained for first awakening sample on Day 2 were averaged for the purposes of statistical time-plot analysis. Time of first awakening sample was plotted at 7.30 am, being the approximate average time value for first awakening sampling.

Full RIA analysis data is included as Appendix 7.1. Excluding mid-sleep wakening samples, 242 saliva samples were assayed. Of these, 10 samples had insufficient saliva for reliable testing. For statistical purposes these samples were referred to as having "missing values", and were analysed as follows:

- where a missing value occurred between two consecutive time values, the average of the previous and the following value was used. For example a missing value at 8.00 pm was calculated by averaging the value at 6.00 pm and the value at 9.00 pm (3 samples);

- where a missing value occurred at 9.00 am on Day 1 of testing, the value obtained at 10.00 am on Day 2 was substituted (2 samples);

- where a missing value occurred at 10.00 am on Day 2 of testing, the value obtained at 9.00 am on Day 1 was substituted (2 samples);

- where a missing value occurred at first final awakening on Day 2, the value obtained at 9.00 am on Day 1 was substituted (3 samples).

Time Sequence Plot (TSP) analysis was used to plot each participant's raw secretion levels and standardised secretion levels. Secretion levels were standardised by dividing each participant's individual time point secretion levels into their maximum secretion level. Visual inspection of the plots indicated a more even on-set of rhythm for the good psychogenic health group, as opposed to a peak/trough patterns for the poor group in terms of both raw secretion levels (comparison of Figure 7.1 (a)&(b) and standardised secretion levels (comparison of Figure 7.2 (a)&(b)).

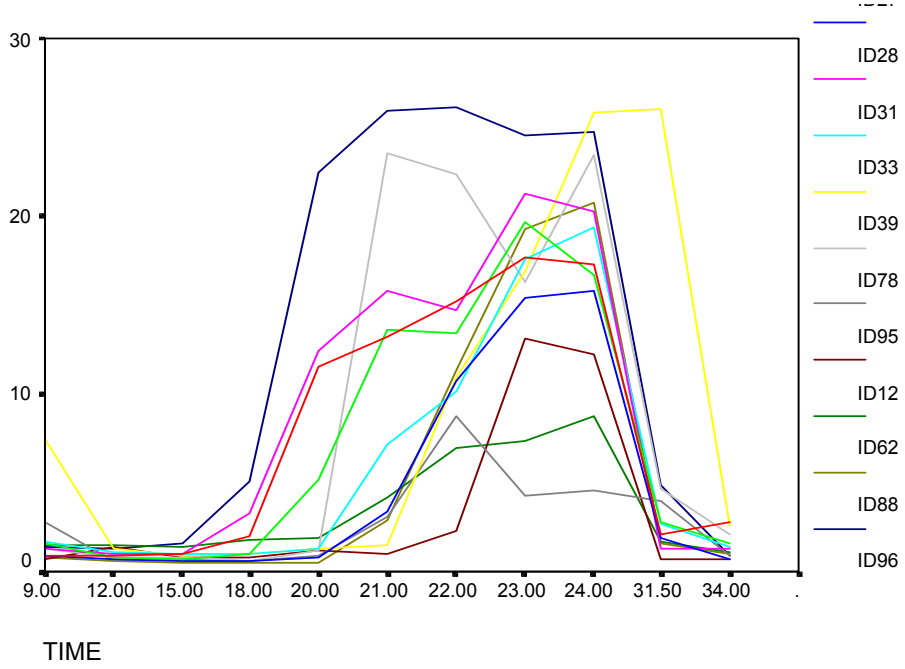

Figure 7.1(a):Time sequence plot showing melatonin secretion levels (pg/mL:vertical axis) for participants assessed as having good psychogenic health

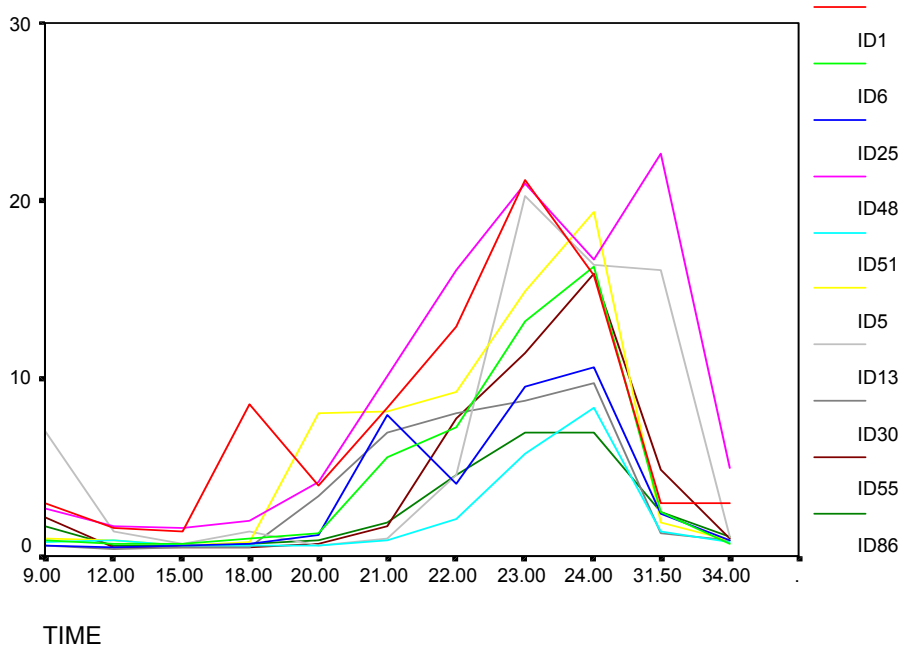

Figure 7.1(b):Time sequence plot showing melatonin secretion levels (pg/mL:vertical axis) for participants assessed as having poor psychogenic health

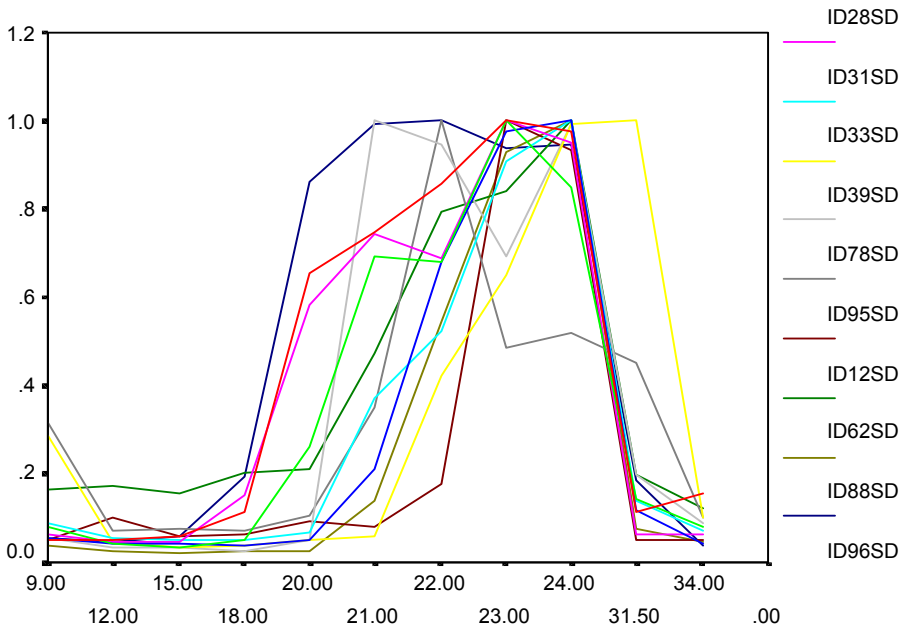

Figure 7.2(a): Standardised TSP showing melatonin secretion levels (pg/mL:vertical axis) for participants assessed as having good psychogenic health

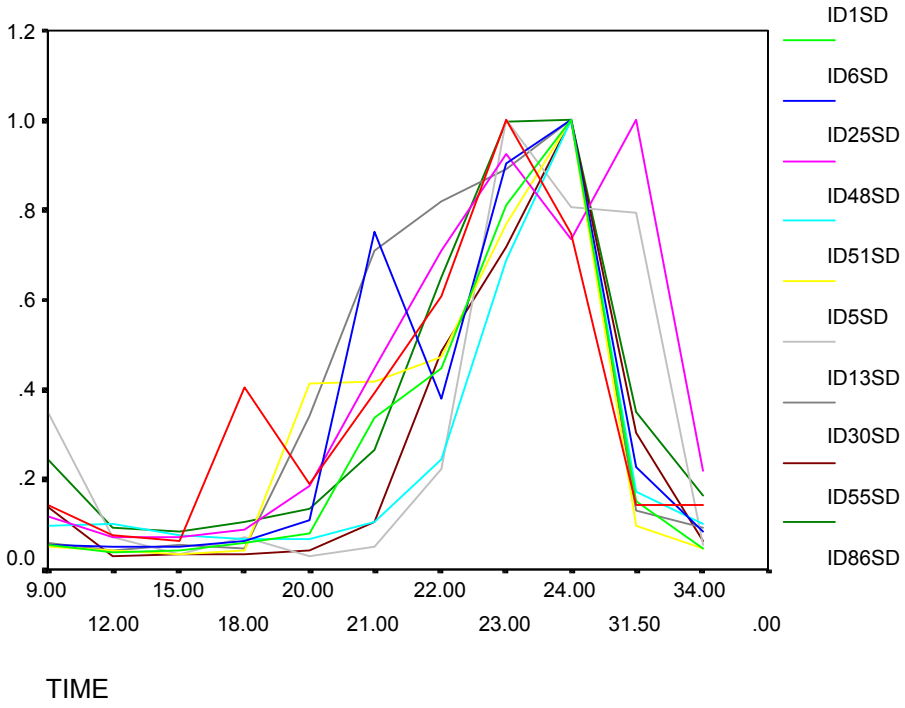

Figure 7.2(b): Standardised TSP showing melatonin secretion levels (pg/mL:vertical axis) for participants assessed as having poor psychogenic health

Previous research has established that evening on-set of melatonin rhythm is significantly higher than daytime rhythm. To confirm this pattern within this study sample, a repeated measures (paired) t-test was used to compare participants' daytime secretion levels with those obtained at midnight. Daytime (baseline) rhythms were calculated by averaging individual secretion levels obtained at 9.00 am, 12 noon and 3.00 pm. Results showed a significant difference between baseline mean values (M = 1.25 pg/mL, SD =.73 pg/mL) and a midnight secretion mean values (M = 15.71 pg/mL, SD = 5.77 pg/mL), where $t(21) = -12.123$, $p = .0001$.

Partial area under the curve (AUC) was then mathematically estimated for all participant values from the 9.00 am sample on Day 1, up to and including the midnight sample. An independent t-test was used to compare AUC results from those participants designated as having good psychogenic health, with those designated as having poor psychogenic health. No significant difference between the two groups ($t(20) = 1.680$, $p = .109$) was found. To assess whether the sample size (N = 22) was sufficiently powerful to detect a statistically significant difference AUC, Cohen's d, was calculated for each AUC value. A resultant effect size of $d = .72$, with an equivalent power of .62 was established, suggesting there was a 62% chance of detecting a significant AUC difference, given a sample size of 22 (Cohen, 1988).

Both the good psychogenic health group and the poor group had participants undergoing natural transition and participants undergoing HRT-assisted transition. However, 2 (natural/HRT) x 2 (good/poor psychogenic health) ANOVAs show no significant interaction between psychogenic symptom frequency scores (PSF) and group membership ($F(1,18)= 1.419$, $p = .249$) or total melatonin secretion levels and group membership ($F(1,18)=.009$, $p = .925$).

Average melatonin values at each sampling time point were calculated for natural and HRT-assisted participants in the good psychogenic health group and natural and HRT-assisted participants in the poor psychogenic health group. Time sequence plots were produced for both the good psychogenic health group (see Figure 7.3(a)) and the poor psychogenic health group (see Figure 7.3 (b)). While the peak secretion level for the good psychogenic health group was visually higher than that for the poor group, the time sequence plots shows a remarkable similarity of profile between natural and HRT-assisted participants in both groups.

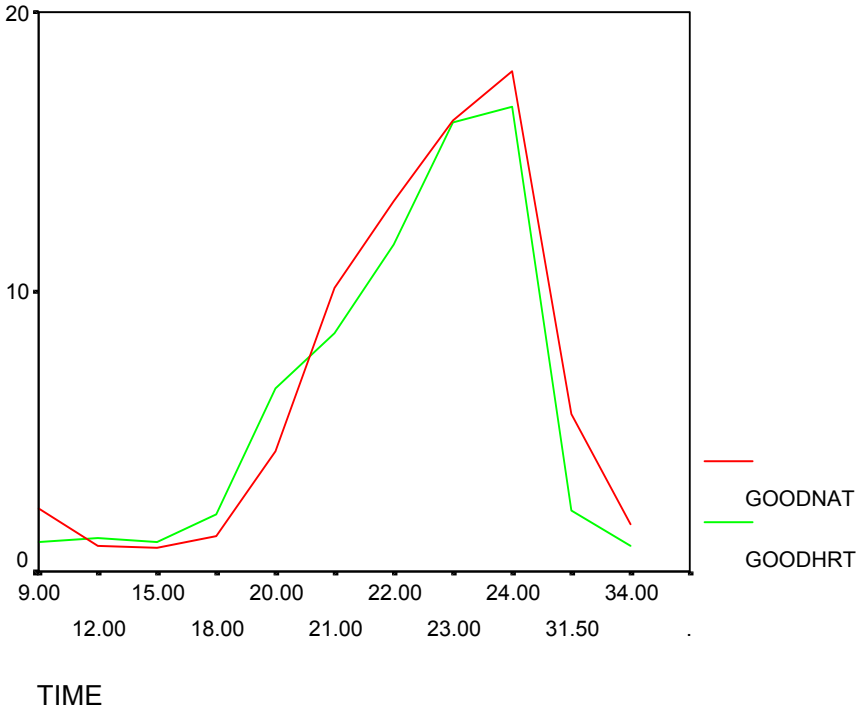

Figure 7.3(a):Average melatonin secretion levels (pg/mL:vertical axis) for natural and HRT-assisted participants assessed as having good psychogenic health

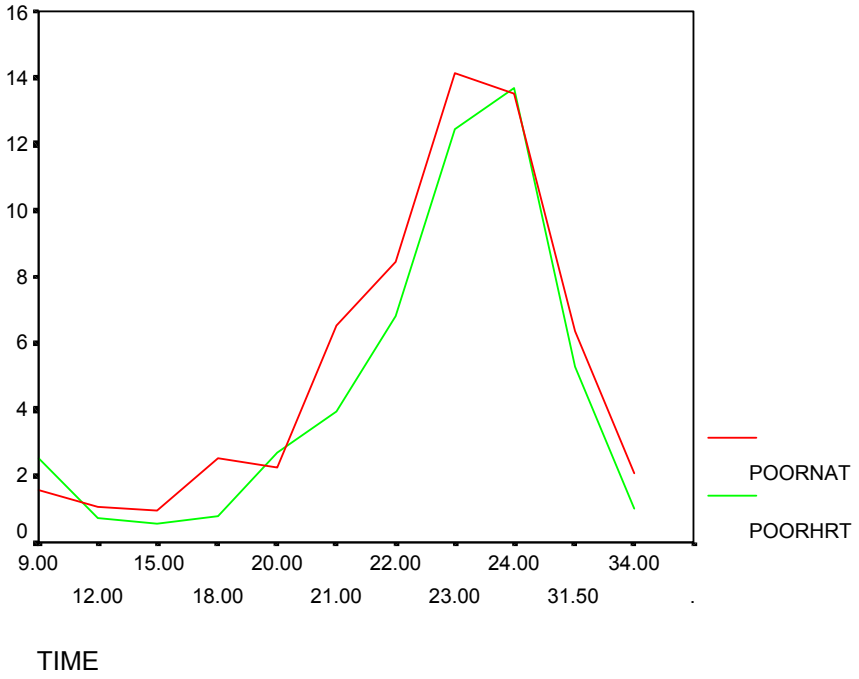

Figure 7.3(b):Average melatonin secretion levels (pg/mL:vertical axis) for natural and HRT-assisted participants assessed as having poor psychogenic health

Average time sequence melatonin values for all participants were then calculated and plotted for comparison between those participants designated as having good psychogenic health (combined natural and HRT-assisted), and those designated as having poor psychogenic health (combined natural and HRT-assisted). As can be seen in Figure 7.4, when comparing participants on the basis of their psychogenic health status, melatonin secretion levels appear similar from 9.00am on Day 1, up to and including 6.00pm, but from 8.00pm onwards those participants designated as having good psychogenic health have visibly higher mean values than participants designated with poor psychogenic health.

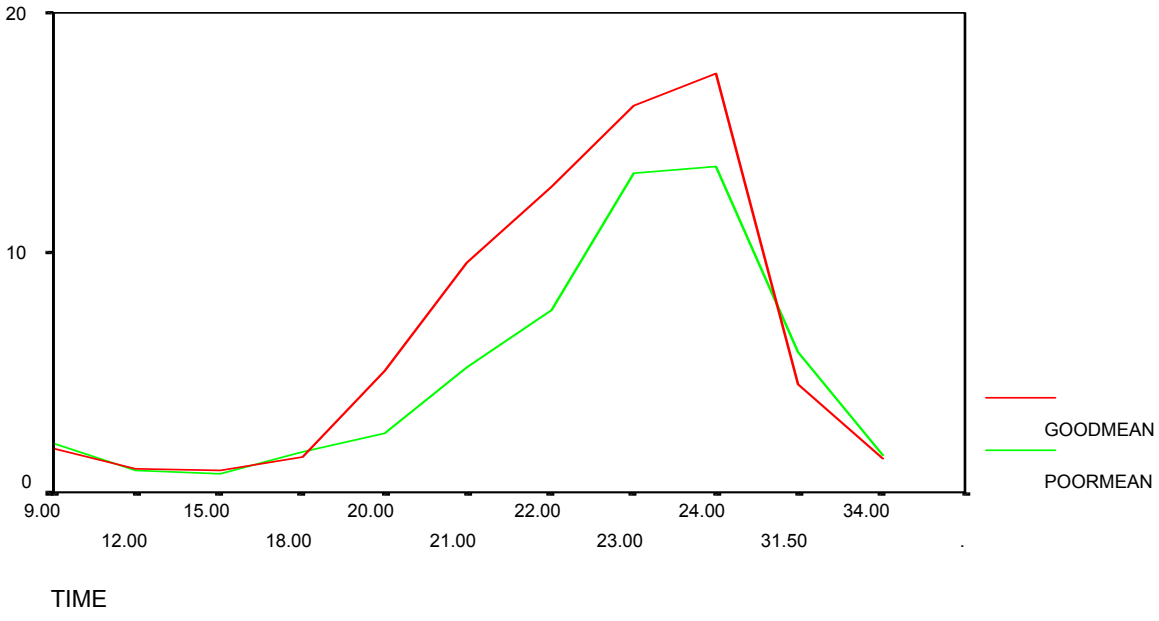

Figure 7.4: Comparison of mean melatonin secretion level pg/mL :vertical axis) for participants assessed as having good or poor psychogenic health

A mixed design split plot analysis was used to establish if any significant difference existed between subject groups, where the between-group factor was designated as 'good' or 'poor' psychogenic health, and the within-subject factor was reported melatonin secretion levels for all participants at hourly intervals from 8.00pm up to and including midnight. Results showed a trend toward a significant difference in relation to the between-group factor ($F(1,20) = 3.24$, $p = .087$. Figure 7.5 shows the estimated marginal means for both good and poor psychogenic health group participants.

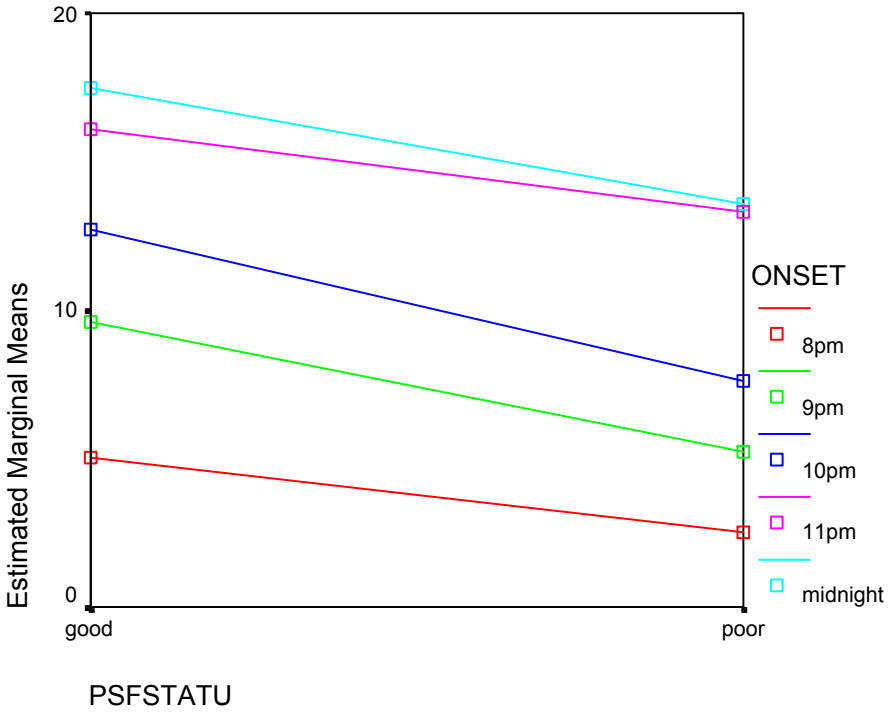

Figure 7.5: Estimated marginal meltonin secretion means (pg/mL) for participants assessed with good and poor psychogenic health

7.3 Exposure to Light:

Light exposure (lux) results from two participants designated as having good psychogenic health, and two participants designated as having poor psychogenic health, were discarded due to PDMD equipment problems. This left a sample pool of 10 participants assessed with good psychogenic health and 8 assessed with poor psychogenic health. Mean lux exposure levels for both groups were calculated at hourly increments from 8.00am on Day 1 up to and including 6.00pm on Day 1. Time sequence graphs were plotted separately for the 3 lux levels (500 lux, 3,000 lux, 10,000 lux) and are shown as Figure 7.6 (a), (b) and (c). For ease of plotting, the mean hourly exposure values were marked at the end of each hourly increment – that is, the value obtained between 8.00am and 9.00am was plotted as the value at 9.00am, etc.

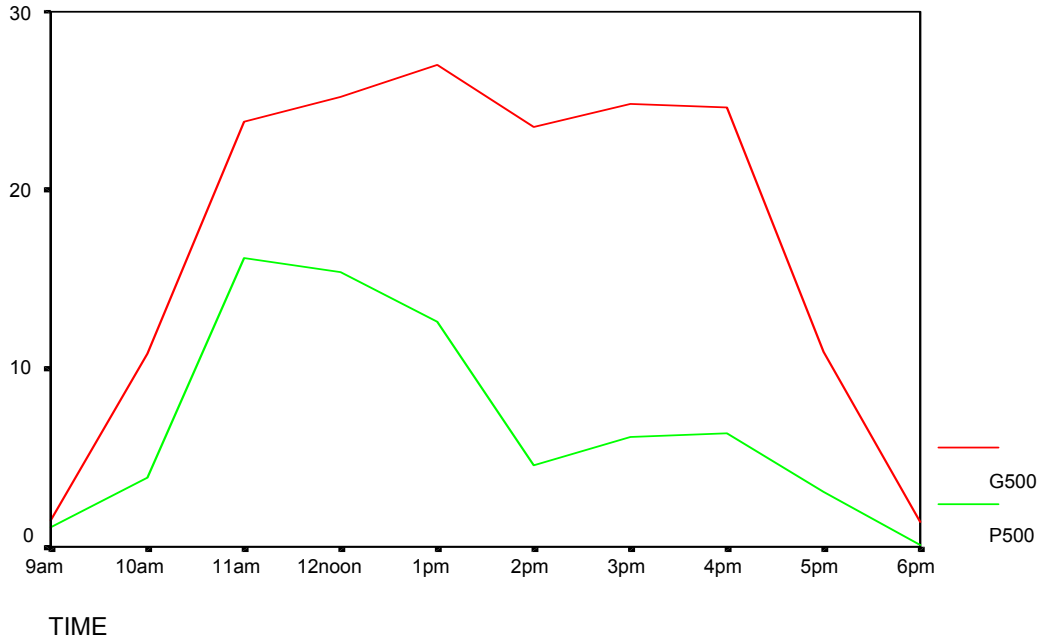

Figure 7.6(a):Comparison in minutes of exposure to lux 500 levels between participants assessed with good (G) and poor (P) psychogenic health

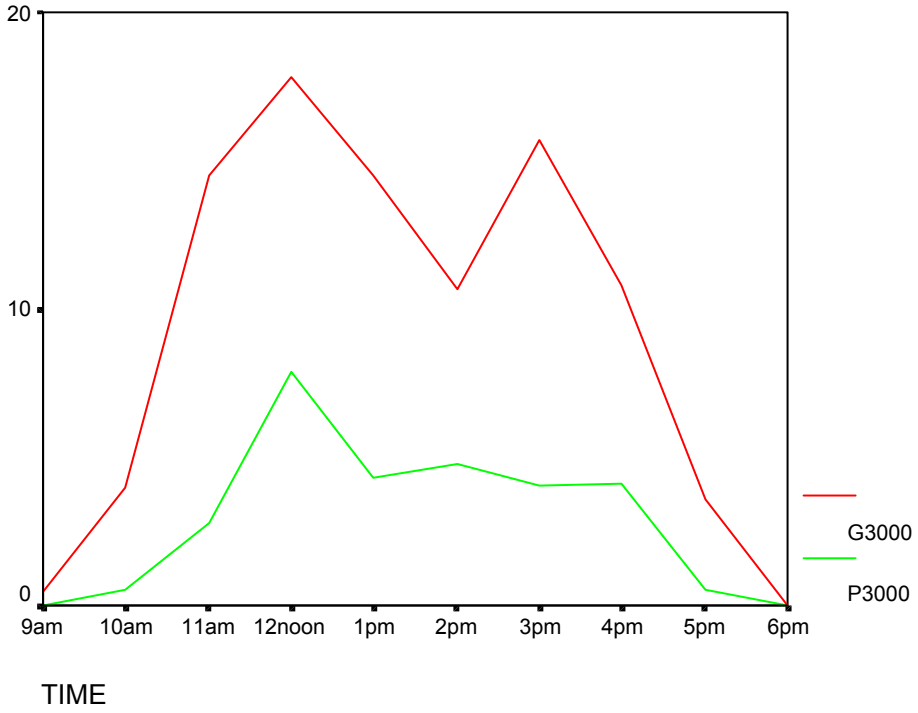

Figure 7.6(b):Comparison of exposure to lux 3,000 levels between participants assessed with good (G) and poor (P) psychogenic health

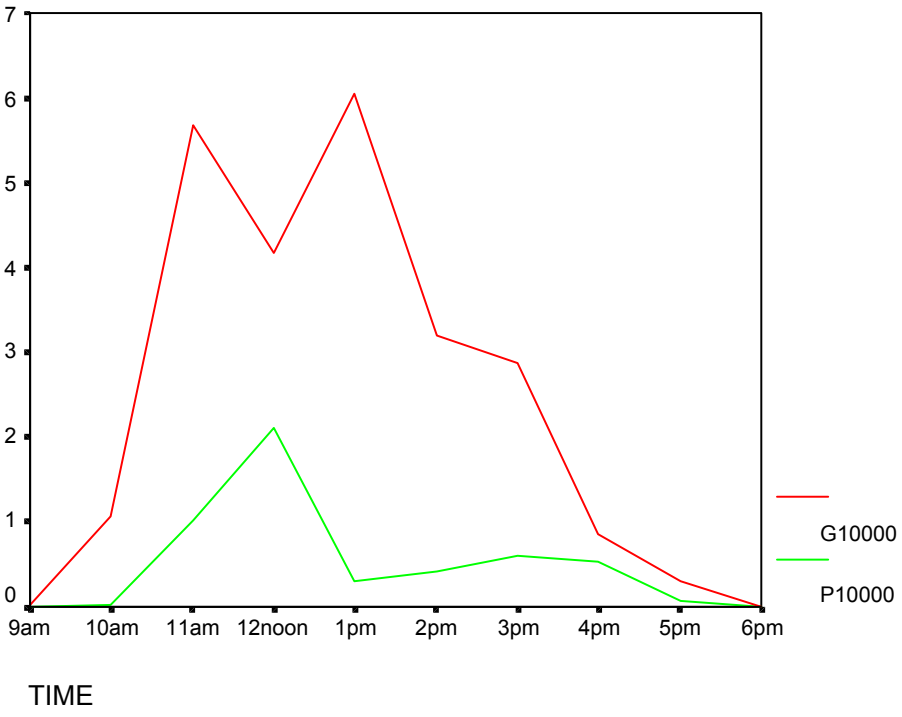

Figure 7.6(c):Comparison of exposure to lux 10,000 levels between participants assessed with good (G) and poor (P) psychogenic health

While the graphs plotted in Figure 7.6 (above), used mean incremental time scores, the in-house software program (LUXVU) also allowed amalgamation of data. Using this data, a single factor Multivariate Analysis of Variance (MANOVA) calculated minutes at each of the three lux levels for each participant. The results showed a significant main effect ($F(3,14)= 4.045$, $p =.029$), where the independent variable was psychogenic status and the dependent variables were minute counts at 500, 3,000 and 10,000 lux values. Descriptive and univariate statistics are shown in Table 7.2.

Table 7.2: Descriptive and univariate statistics for exposure to lux levels (500, 3,000 and 10,000) for Study 2 participants

Lux Level	PSF Status	No.	Mean (Mins)	SD	F-Value(df)	p-value
500	Good	10	191.70	81.80		
	Poor	8	77.63	58.79	10.95 (3,14)	.004
3,000	Good	10	103.30	45.92		
	Poor	8	32.38	33.52	13.33 (3,14)	.002
10,000	Good	10	26.50	26.02		
	Poor	8	5.75	8.53	4.64 (3,14)	.047

7.4 Quality of Sleep:

As trouble sleeping featured as both the most frequently reported symptom, and the highest in terms of severity of symptom impact, Study 2 also monitored participants' subjective and objective sleep patterns over a period of five consecutive nights. Quality of sleep was assessed both subjectively (using sleep logs) and objectively (using physiological data monitoring devices). Of the 22 participants initially involved in Study 2,

PDMD data was excluded from analysis for three participants in the good psychogenic health group, and from one participant in the poor psychogenic health group. These exclusions were due to problems with PDMD monitoring devices that gave insufficient and/or unreliable data over the monitoring period. To ensure an equitable comparison between subjective and objective sleep monitoring, the sleep log data from these four participants were also excluded from analysis. This left a study sample size of 18, with nine participants classified as having good psychogenic health and nine participants classified as having poor psychogenic health.

Sleep log questions were designed to give mathematically scaleable mean values for the following sleep parameters:

- Grade of Normality (mean summation of Q#2, Q#4, Q#9): where normality of sleep equated to a score of 6 (range = 0 – 12).

- Sleep Efficiency (mean summation of Q#3, Q#8): where the higher the score, the less efficient the sleep (range = 0 – 8).

- Sleep Fragmentation (mean summation of Q#5. Q#7): where the higher the score, the more fragmented was the sleep (range = 0 – 8).

Independent t-tests failed to find any significant difference (p = >.05) between participants assessed as having good or poor psychogenic health in relation to their subjective perception of normality of sleep during the study period, nor their subjective sleep efficiency or sleep fragmentation scores (see Table 7.3).

Table 7.3: Descriptive and inferential statistics for subjective sleep parameters for Study 2 participants

Sleep Parameter value	PSF Status	No.	Mean	SD	t-value (df)	p-
Grade of Normality	Good	9	5.84	0.52		
	Poor	9	6.37	0.09	-1.447 (16)	.167
Sleep Efficiency	Good	9	2.19	1.46		
(SSE)	Poor	9	3.04	1.93	-1.064 (16)	.303
Sleep Fragmentation	Good	9	2.65	1.46		
(SSF)	Poor	9	3.13	1.41	0.709 (16)	.489

As previously outlined, objective sleep was measured over a five night period, and the raw data was converted into four correlating variables (mean activity levels [MAL], movement index [MI], mean immobility periods [MIP] and fragmentation index [FI]). A single factor Multivariate Analysis of Variance (MANOVA) failed to report any significant main difference (p = >.05). However, again in each case the mean values differed toward the 'poor' psychogenic group having a worse quality of sleep than their 'good' group counterparts (see Table 7.4). Given the small number of participants in each group, it is possible that the sample

size lacked sufficient power to establish any statistically significant difference at the given alpha levels.

Table 7.4: Descriptive and univariate statistics for objective sleep parameters for Study 2 participants

Sleep Parameter	PSF Status	No.	Mean	SD	F-value(df)	p-value
Mean Activity Levels (MAL)	Good	9	0.18	0.13		
	Poor	9	0.23	1.53	0.402(4,13)	.535
Movement Index (MI%)	Good	9	2.88	1.10		
	Poor	9	3.48	1.53	0.935(4,13)	.935
Mean Immobility Periods (MIP)	Good	9	15.18	6.56		
	Poor	9	12.51	3.08	1.219(4,13)	.286
Fragmentation Index (FI%)	Good	9	21.77	2.69		
	Poor	9	20.56	2.78	0.881(4,13)	.362

7.5 Nocturnal Peripheral Body Temperature:

Equipment problems led to the exclusion of four participants from the good psychogenic health group and one participant from the poor psychogenic health group. Peripheral body temperature data were therefore analysed from eight participants assessed as having good psychogenic health, and nine participants assessed as having poor psychogenic health. As in the analysis for sleep quality (Section 7.4), subjective data from sleep logs that recorded incidence and severity of night sweats/flushes were also excluded from analysis for those participants whose objective peripheral body temperature (PBT) data were excluded.

Initially, 16-second epoch peripheral body temperature data for the nocturnal periods was converted (using TEMPVU) over the study nights into average minimum and average maximum peripheral body temperature values. Independent t-tests reported no significant differences (p = >.05) between the average minimum PBT for both good and poor psychogenic health groups, or for average maximum PBT (see Table 7.5).

Table 7.5: Descriptive and inferential statistics for minimum and maximum nocturnal peripheral body temperatures for Study 2 participants

Variable	PSF Status	No.	Mean	SD	t-value (df)	p-value
Min. Nocturnal PBT	Good	8	29.01	0.07		
	Poor	9	29.00	0.07	0.295 (15)	.772
Max. Nocturnal PBT	Good	8	36.00	0.40		
	Poor	9	36.34	0.48	–1.637 (15)	.122

As the TEMPVU software program also allowed for statistical calculation of hours spent at any given 1°C incremental value, the two groups were then compared on hours recorded at 35-36°C. This statistical value was the nearest incremental hourly value to the maximum PBT attained by all 17 study participants. As shown in Table 7.6, results indicated a strong trend toward a significant difference between good and poor psychogenic health groups, with the poor psychogenic health group

spending longer nocturnal hours at the maximum PBT than their good psychogenic health counterparts.

Table 7.6: Descriptive and inferential statistics for time spent at maximum nocturnal peripheral body temperature (35º-36ºC) attained by all Study 2 participants

Variable	PSF Status	No.	Mean(Hrs)	SD	t-value(df)	p-value
Hours at 35-36º C	Good	8	2.34	0.75		
	Poor	9	3.23	1.00	- 2.073 (15)	.056

Sleep logs allowed participants to record the number of hot flushes/sweats that occurred during each of the five study night periods, and to assign a severity rating to each flush/sweat (where 1 = uncertain flush, to 4 = severe flush). Chi-square analysis of frequency of flushes recorded between the two psychogenic health groups showed the poor psychogenic health group recorded a significantly greater number of flushes during the study period than did the good group, where χ^2 = 16.49 (good = 23, poor = 60), $\underline{p}$ = .0001.

Severity scores for each flush/sweat were accumulated and then averaged over the five study nights for all participants. An Independent t-test indicated a statistically significant difference between overall severity of flushes for the good psychogenic health group (M = 2.16, SD = 1.83) and the poor psychogenic health group (M = 9.40, SD = 4.83), $\underline{t}(81)$ = -9.903, $\underline{p}$ = .0001.

Given the small sample size (N=17) and the possible ensuing lack of statistical power, these results highlight the strength of the statistic between the two groups in terms of both frequency and severity of impact of nocturnal flushing episodes.

7.6 Summary of Results from Study 2:

- Twenty-two transitional women took part in Study 2. Twelve women (8 = Natural, 4 = HRT-assisted) with the lowest psychogenic frequency scores (PSF) were assigned to the good psychogenic health group. Ten women (5 = Natural, 5 = HRT-assisted) with the highest PSF scores were assigned to the poor psychogenic health group.

- There was no statistically significant difference between the two groups in terms of age, transitional status, or method of transition. There was a significant difference in PSF scores ($\underline{p}$ = .0001) in terms of their assigned status within the good or poor psychogenic health groups.

- Visual inspection of combined individual melatonin secretion levels (using Time Sequence Plots) indicated a more even on-set of rhythm for those assigned to the good psychogenic health group, than their poor psychogenic health assigned counterparts.

- A mathematical estimate of partial area under the curve (9.00 am to midnight) failed to show any statistically significant difference between the two groups. However, subsequent application of Cohen's d and associated power tables indicated only a 62% chance of finding a statistically significant difference, should one exist, at alpha = .05 given a sample size of 22.

- No significant interaction (2x2 ANOVA) was found in PSF scores for participants in terms of either method of transition (natural/HRT-assisted) or psychogenic health (good/poor).

- When compared visually, time sequence plots for natural and HRT-assisted participants assigned to the good psychogenic health group showed very similar profiles. This similarity in TSP profile was also evident when comparing natural and HRT-assisted participants assigned to the poor psychogenic health group.

- No significant interaction (2x2 ANOVA) was found for melatonin secretion levels for participants in terms of either method of transition (natural/HRT-assisted) or psychogenic health (good/poor).

- Visual comparison of average melatonin secretion values for both the good and poor psychogenic health groups (combined natural

and HRT-assisted participants) showed differences in time point profiles. Time sequence plots at each saliva sampling point showed that, while the baseline results were almost identical, the good psychogenic health group commenced on-set of at an earlier time point, and retained their higher average secretion levels up to and including the midnight sample in comparison to their poor psychogenic health group counterparts.

- Split-plot analysis reported a significant trend toward difference for all time point on-set of rhythms from 8.00 pm up to and including midnight, with the greatest difference occurring at the 10.00 pm time point. At all time points, the good psychogenic health group had higher average melatonin secretion levels than their poor psychogenic health counterparts.

- Results from exposure to light monitoring, undertaken concurrently with the melatonin secretion level monitoring (9.00 am to midnight), showed statistically significant differences at each lux level (500, 3,000 and 10,000). With a main effect of $\underline{p} = .029$, the good psychogenic health group had significantly greater exposure to light at all three lux levels than their poor psychogenic health counterparts.

- Within both objective and subjective measures of quality of sleep, the good psychogenic health group had higher mean values in terms of better quality of sleep. However, no statistically significant difference for any of the measures was established at alpha = .05.

- In terms of peripheral body temperature, there was no statistically significant difference between the two groups in terms of either their average minimum or average maximum PBT over the study period. However, a strong trend ($p = .056$) toward significant difference was established for hours spent at the nearest incremental maximum PBT (35-36°C). The poor psychogenic health group trended toward spending significantly greater nocturnal hours at 35-36ºC PBT than did their good psychogenic health counterparts.

- Participants classified within the poor psychogenic health group reported a significantly higher number of hot flushes/sweats during the study period than the good psychogenic health group. They also viewed the severity of these nocturnal hot flushes/sweats as significantly more severe than their good group counterparts.

CHAPTER 8

DISCUSSION

"For men, there are two inescapable realities in life

Death and Taxes;

For women, there are three

Death, Taxes and THE MENOPAUSE"

(Jo Wainer, 1998)

In the body of this thesis, Studies 1 and 2 were presented as two separate research studies (Chapters 2, 3 & 4, and Chapters 5, 6 & 7 respectively). Each study had its own literature review, rationale/aims, methodology and results section. Chapter 8 combines the results from both studies in an integrated discussion, which argues that:

- There is no evidence to suggest that choice of transition (natural/HRT-assisted) modifies either the severity of impact of menopausal symptoms, or the predictive value of psychosocial factors within the transitional environment.

- Regardless of the frequency of menopausal symptoms, the severity of their impact in terms of maintaining a normal lifestyle, can be predicted by factors within the psychosocial environment.

- The best predictor of impact of overall menopausal symptom severity is psychosocial adjustment within the domestic environment domain. General psychological health best predicts impact of psychogenic symptom severity.

- There is a permissive link between earlier and higher melatonin evening on-set secretion levels and lower frequency of psychogenic symptoms experienced by women undergoing menopausal transition, which is again not influenced by method of transition (natural/HRT-assisted).

- There is a permissive link between greater exposure to natural light at 500, 3,000 and 10,000 lux and lower psychogenic symptom frequencies.

- While "trouble sleeping" is commonly cited as one of the most frequent and troublesome menopausal symptoms, it should not be viewed in isolation from other psychogenic symptoms, but rather as contributing to an aggregated effect within the psychogenic symptom cluster.

- Nocturnal hot flushes/sweats, while more frequently experienced by women with a higher incidence of psychogenic symptoms do not, in themselves, result in poorer subjective or objective sleep quality when compared to the sleep quality of women with a lower incidence of psychogenic symptoms.

8.1 Menopausal Status of Study Population:

Seventy percent (N=50) of participants were currently undergoing natural transition while 30% (N=21)) were using HRT to assist transition. As many women move between non-use of HRT and use of HRT during their menopausal transition period, it is difficult to find data to establish whether 30% is a reliable average usage figure for a community-based sample in Australia. One of the few large community-based studies that did include data from women using HRT, was the North American retrospective Rancho Bernado Study (von Muhlen, et al., 1995). Von Muhlen, et al. noted that when asking participants to recall HRT usage, 42% of participants recalled some prior use, with 27% still using some form of HRT at the time of retrospective sampling. A recent Australia study (France, et al., 1997) quoted a usage rate of 47% (N=121/258), with 14% (N=36/258) being previous users. This compares to 12% (N=248/2001) of women who were noted as using HRT when initial recruitment was made for the cross-sectional study of the Melbourne Women's Mid-Life Health Project (MWMHP) (Dennerstein, et al 1993). While 12% seems somewhat low, the MWMHP classified current HRT users separately from women who had undergone surgical menopause (n=429/2001). As all these women were subsequently excluded from the study, no details were given with regard to the percentage of women who had undergone surgical menopause but were currently using HRT. One community-based study that did report such a breakdown was the

Massachusetts Women's Health Study (MWHS) were it was noted that approximately 50% of women who had undergone surgical menopause were currently using HRT to assist with symptoms of transition. If this percentage were applied to the MWMHP, then their rate of HRT usage would be in the order of 23%. In the current study, four participants had undergone a simple hysterectomy and all were using HRT to assist their menopausal transition. Given the above, it is reasonable to suggest that the 30% of participants in the current study who were using HRT to assist their transition reflects a representative measure of average HRT usage within the Australian menopausal community.

To assess the reliability of the symptom profile of the study population, symptom frequency data was compared to data obtained from large community-based studies. Cumulative sum analysis of menopausal symptom frequency scores (MSF) showed the top ten most frequently reported symptoms in the present study to be in line with those reported in the Melbourne Women's Midlife Health Project (Dennerstein, et al., 1993), where a similar symptom list was used. The type of symptoms in the top ten frequency list were also in line with the Massachusetts Women's Health Study (McKinlay, et al., 1992), the Rancho Bernardo Study (von Muhlen, et al, 1995) and the USA National Ambulatory Medical Survey (cited in Shaver & Paulsen, 1993), where problems with sleep, fatigue, mood, flushes/sweats

and skeletal discomfort were among the most frequent symptoms reported by study participants.

8.2 Method of Transition (Natural/HRT-Assisted) in Relation to Menopausal Symptoms:

Research opinion is still undecided as to the efficacy of HRT, especially with regard to its use for alleviation of psychogenic-type menopausal symptoms (see Chapter 2.6). Thus this study compared its HRT and non-HRT using participants on a wide range of measures. The results of a MANOVA analysis indicated that there was no significant difference between HRT users and non-users (univaritate p=.761) in terms of their self-reported assessment of the severity of impact (MSS) of the 33 symptoms listed on the Health Symptom Checklist (HSC). Nor was there any significant difference in mean scores for measures assessing their pre-menopausal history (MH), the effect of premenstrual tension on mood (PMT), global sleep quality (PSQI), general psychological health (GHQ-30) or total psychosocial adjustment (PAIS-T).

The three main psychosocial predictors that emerged from Study 1 will be discussed in greater detail in Section 8.3. However, all three of the measures (PAIS-T, PSQI and GHQ-30) allowed further organization of raw scores into good, fair and poor categories (PAIS-T and PSQI) or good and poor psychological health (GHQ-30). Analysis again showed no significant

differences in terms of category group means (independent t-tests) or frequency in category membership (chi-square) when compared in terms of method of transition (natural/HRT-assisted).

Five psychogenic symptoms (trouble sleeping, lack of energy, sad/downhearted, difficulty in concentration, nervous tension) were embedded in the HSC, as were two nocturnal thermoregulatory symptoms (hot flushes/sweats at night, cold sweats at night). With regard to the psychogenic symptoms, an independent t-test with method of transition (natural/HRT-assisted) as the independent variable and total psychogenic symptom scores (PSS) as the dependent variable failed to find any significant difference between participants in terms of their method of transition. More surprising was the similarity in percentages of participants who reported maximum debilitation scores (where a maximum score of three equated to a major symptom effect in terms of maintenance of normal lifestyle). As shown in Figure 4.1 (Chapter 4), HRT users and non-users were equally distributed in terms of all five psychogenic symptoms.

As HRT is commonly advocated for alleviation of thermoregulatory symptoms, it would have been expected that women using HRT would have had either less frequent reporting of nocturnal sweats/flushes or would report their impact as being less severe. Again, this was not the case, with

independent t-tests showing no significant differences between women using HRT and their non-using counterparts in terms of either frequency of symptom reporting, or severity of symptom impact.

Many of the above findings have been supported by a New Zealand study published after the completion of data collection and analysis for the present study. Stephens and Ross (2002) also used questionnaire-based research to investigate the relationship between HRT use and psychological symptoms in a randomly selected sample of 494 New Zealand women between 45 and 60 years of age. Their percentage of HRT users was similar to that reported in this study, with 25% current HRT users, 14% past users, and 59% who had never used. When citing reasons for use, 41% of current users cited control of moods and psychological distress during transition. Results showed no significant differences between HRT users and non-users in terms of psychological well-being (assessed by the Positive & Negative Affect Scale, and the GHQ-12, a shortened version of the GHQ-30 used in the present study). In terms of women with higher than normally expected levels of psychological distress, Stephens and Ross reported no significant difference in levels of positive and negative affect, or psychological distress, between HRT users and non-users.

While Stephens and Ross (2002) did not compare participants in terms of their levels of psychosocial adjustment, Roberts et al. (1992) did so. The main aim of their study was to establish whether HRT regimes could improve the overall psychosocial adjustment of women in mid and late transition. Over an 18-month period participants received continuous HRT, cyclic HRT or calcium (placebo group). In addition they each attended a 6-monthly consultation with a gynecologist where they could discuss all questions relating to their menopausal transition. Using PAIS-T to assess overall psychosocial adjustment Roberts et al. reported an improved level of psychosocial adjustment at the end of their study period in all three groups that could not be accounted for by the HRT intervention regime.

The results of Study 2 will be discussed in greater detail later in this chapter. However, with regard to HRT usage, the results from the present study support those of Cagnacci, et al. (2000), with a 2 x 2 ANOVA showing no significant differences in total melatonin secretion levels between HRT users and non-users assigned to the good psychogenic health group, and HRT users and non-users assigned to the poor psychogenic health group. Unlike Cagnacci, et al. this study also compared average melatonin secretion levels obtained at all melatonin time sampling points. As could be seen in Figures 7.3(a) and 7.3(b) in Chapter 7, Time Sequence Plot analysis revealed a remarkable similarity in melatonin profiles between HRT users and non-

users who were assigned to the good psychogenic health group, and also between HRT users and non-users assigned to the poor psychogenic health group. Both HRT users and non-users in the good psychogenic health group had higher average secretion levels than HRT users and non-users in the poor psychogenic health group at all on-set evening sample times from 8.00 pm up to and including midnight.

In discussing the validity of the findings in relation to the method of transition used (natural/HRT-assisted), the following points should be noted:

- **Expectancy effect:** As none of the participants in either Study 1 or Study 2 were aware that their method of transition was of any interest in terms of the study protocol, there is no reason to suspect that these results have been influenced by expectancy effect.

- **Bias in symptomatic profile:** It could be argued that the majority of the participants using HRT were women who were currently experiencing symptoms that were not alleviated by HRT. If their non-HRT using counterparts were predominantly women who were also experiencing quite severe menopausal problems, this could account for the failure to find any significant differences between the two groups in terms of symptom severity or psychosocial health. Thus the study results should have reflected a

sample population in which both symptom frequency and impact of symptom severity and psychosocial health was skewed toward the negative end of the scale. This was not borne out by study results. For example, the majority of participants displayed good or fair psychosocial health (79%) and good psychological health (65%). With regard to sleep problems, which were the most frequently reported symptom, 55% of participants still displayed good to fair global sleep quality as assessed by the PSQI.

- **Study 2 selection criteria:** When selecting participants for Study 2, method of transition (natural or HRT-assisted) was not taken into account. Participants were selected solely on the basis of psychogenic symptom frequency scores. From a pool of 44 women from Study 1, women with the 13 highest and the 13 lowest psychogenic symptom frequency scores were invited to participate in Study 2.

8.3 Predictive Value of Psychosocial Factors during Menopausal Transition:

One of the main aims of Study 1 was to establish (a) the predictive value of psychosocial factors in relation to the severity of impact of menopausal symptoms (see 8.3.1 below), and (b) whether there was a distinction between predictors of sub-cluster symptoms (ie. psychogenic and nocturnal thermoregulatory sub-clusters) and predictors of overall symptom severity (see 8.3.2 and 8.3.3 below). Stepwise linear regression modeling

was used, with general psychological health (GHQ-30), psychosocial adjustment (PAIS), global sleep quality (PSQI), pre-menstrual history (MH), and effect of pre-menstrual tension on mood (PMT), as the predictor variables.

8.3.1 Predictors of Overall Menopausal Symptoms Severity.

In this model, the combined symptom severity score (MSS) for all symptoms experienced from the 33-item HSC was used as the dependent variable. Of five predictor variables used, MH and GHQ-30 were excluded as not contributing to model variance. The largest contributor to the total explained variance (48.2%) was psychosocial adjustment (PAIS-T) that contributed 28.6%. Global sleep quality (PSQI) contributed 15.0%, and effect of pre-menstrual tension on mood (PMT) contributed a further 4.5%.

PAIS-T gives a combined score for seven relatively independent dimensions of psychosocial adjustment (Morrow, et al., 1978). While used widely within chronic illness groups, only one other study (Roberts, et al., 1992) has, as yet, used PAIS to assess psychosocial adjustment within menopausal population. As in the Roberts et al. study, this study also found that, in the main, transitional women exhibited good to fair levels of psychosocial adjustment. However, this study found 21% (N=15) of participants exhibited poor adjustment, as opposed to the 14% recorded at

the commencement of the Roberts et al. 18 months study. Without further research using this measure within a transitional population, it is not possible to say whether 21% reflects an accurate assessment of poor psychosocial adjustment levels within a general transitional population. The overall group mean score for PAIS-T (M = 37.30, SD = 19.81) was higher than the group mean of the calcium (placebo) group reported by Roberts et al. (M = 22.3, SD = 13.2), suggesting a poorer overall level of psychosocial adjustment. However, in terms of comparison to other chronic illness groupings, the group mean was lower than that of a mixed gender population of chronic hemodialysis patients (M = 49.5, SD = 22.88) reported by Kaplan De-Nour (1982), and in line with that of females with narcolepsy (M = 37.19, SD = 22.8) reported by Bruck (2001).

Regardless of the variation in PAIS-T means between this study and that of Roberts, et al. (1992), both studies reported the highest domain mean scores as those for health care orientation. In the present study, when grouped into good, fair and poor levels of psychosocial health, health care orientation was ranked highest in terms of domain means scores by all three groups. It could be argued that perception of quality of health care information and the way in which health care professionals address related problems would be a major concern to any chronic illness group. However, when comparing the seven PAIS domain mean scores within cardiac, mixed

cancer, diabetes and narcolepsy populations Bruck (2001) noted that only the mixed cancer and the narcolepsy groups reported health care orientation has having the highest of the seven PAIS domain mean scores.

In discussing their results, Roberts, et al. (1992) concluded that participation in a research program focusing specifically on menopause-related concerns and the availability of a 6-monthly consultation with a gynecologist led to the observed improvement in the psychosocial adjustment of their participants. At face value, the results of the present study would support those of Roberts, et al. that menopausal women do not feel they are receiving sufficient information or support from their medical practitioners during their transition.

While comparing domain mean scores, Roberts et al. (1992) did not explore which of the seven PAIS domains most contributed to the total PAIS score, regardless of the assessed level of psychosocial health. The present study did so, having first established reliability (Cronbach's alpha .083) and a normal distribution of test results (K-S, $\underline{p}$>.05). This model analysis showed that the PAIS domain that contributed most to participants overall level of psychosocial adjustment was the domestic environment domain (beta = .265). This domain encompasses the way in which the immediate family adapts to the needs of the transitional woman, both in terms of relationships

and communication. The domains measuring psychological distress (beta = .245) and sexual relations (beta .219) were the second and third highest contributors. No previous literature has specifically examined the effects of the domestic environment in terms of the psychosocial adjustment of women during their menopausal transition. However, Huerta et al. (1995) did examine the association between symptoms at peri-menopause with attitudes toward sexuality, lifestyle and family function in Mexican women. As outlined in Chapter 2.5, Huerta et al. also noted the important changes within the family structure that can occur at or around the time of menopausal transition. While suggesting that the interaction of family function with menopausal symptoms should be explored in a more specific study, they noted that depression was negatively associated with husbands who assumed the role of providers of what they termed "permissions and authority". The empty nest syndrome and non-specific symptoms of depression were also associated with a poor affective involvement with the marital partner.

8.3.2 Predictors of Psychogenic Symptom Severity:

Within the psychogenic symptom cluster, trouble sleeping had been reported in previous studies as being among the most frequent and problematic of all menopausal symptoms. In the present study it was the most frequently reported symptom, with 79% of all participants recording at least one occurrence over a prior 14-day sampling period. In terms of the

severity of impact, it was again the highest reported symptom, with some 31% of participants viewing trouble sleeping as debilitating in terms of maintenance of their normal lifestyle.

As one of the predictor variables in this study measured global sleep quality (PSQI), it could have been expected that this measure would considerably contribute to the amount of explained variance in the predictive model for psychogenic symptom severity. This was not the case in this study. Global sleep quality (PSQI) added only 5.4% of variance to the model, with general psychological health (GHQ-30) accounting for the major predictive variance of 40%. Recalled effect of pre-menstrual tension on mood (PMT) contributed 9.3% of model variance, with a further 3.0% accounted for by total psychosocial adjustment (PAIS-T).

As only two of the 30 questions in the GHQ-30 touched on issues relating to sleep, the small amount of variance (5.4%) contributed by global sleep quality (PSQI) would not appear to be accounted for by the GHQ-30 "picking up" the impact of quality of sleep within the psychogenic symptom cluster. Causal links between problems with sleep and depressive symptoms tend, within past and present research, to follow the chicken-and-egg argument. Studies such as Shaver and Paulsen (1994) and Libbus et al. (1995) argue that poor sleep quality and persistent fatigue in mid-aged

women may be the antecedent of mild to moderate depression. Other researchers such as Mendlewicz et al., (1983) have theorized that alterations in the circadian rhythms for plasma, pituitary and pineal hormones associated with symptoms of depression may in themselves lead to desynchronisation of other circadian rhythms. Referred to as the internal coincidence model, this theory has received more recent support with research reporting improved sleep in bipolar sufferers being linked to the phase delaying effects of on-going lithium treatment on biological rhythms leading to better synchronisation of the sleep-wake cycle (Benedetti, et al. 2001).

While the results in this study cannot further the argument in favour of the primacy of either the chicken or the egg, they do suggest that quality of sleep should not be viewed in isolation from, or largely contributing to the onset of other psychogenic symptoms. Rather, the results suggest that psychogenic symptoms should be viewed as an aggregate, where the general psychological health of transitional women at the time of their transition mediates the severity of the impact of these symptoms.

Within this context, the word 'transition' suggests a continuous movement from a beginning to an end. In the present study, participants were classified in three transitional stages. Briefly, women who had commenced transition, but had not achieved 12 consecutive months

amenorrhoea were designated as in early transition, while those with 12 to 24 months amenorrhoea were designated as in mid transition. Women with more than 24 months amenorrhoea, but who were still experiencing menopausal symptoms made up the late transition group. MANOVA analysis found no significant difference in terms of mean scores for the GHQ-30, PMT, PSQI or PAIS-T in terms of transitional status. However, of the 71 participants in Study 1, 25 (35%) displayed poor psychological health when assessed in terms of the best threshold score (39 plus) for the GHQ-30. At face value 35% represents a high percentage figure for a community-based population not primarily sourced from either clinical or help-seeking venues. As previously discussed (Section 8.2), HRT users and non-users were similarly represented within the group scoring poorly on the GHQ-30. However, participants were not equally distributed in terms of transitional status. A Kruskal-Wallis K samples test found that significantly more women with poor psychological health were in the early transition group than in either the mid or late group. These results, in part, are in line with those of Dennerstein et al. (1997) who also noted significantly higher levels of negative affect in women in early transition when compared to their pre-menopausal counterparts. However, their highest reported levels of negative affect occurred in participants within the 12 to 24 month amenorrhoea group, which was not in accord with the results from the present study.

8.3.3 Predictors of Nocturnal Thermoregulatory Symptom Severity:

Nocturnal hot flushes/sweats in a prior two-week period were reported by 70% of study participants, with 21% according a maximum debilitation score in terms of the severity of impact of these symptoms. They are often anecdotally linked to poor sleep quality by many transitional women. McKinlay et al. (1992) noted that insomnia was twice as likely to be self-reported by women who also self-reported hot flushes/sweats, while Hunter and Liao (1995) reported that 40% of their study population who experienced night flushes/sweats also reported sleep disruption and resultant tiredness. As outlined in Chapter 2.4, a number of links have been established between sleep architecture and nocturnal flushing episodes, including longer REM latencies and lower sleep efficiencies (Shaver et al., 1988), significantly more sleep stage changes with increased Stage 4 sleep suggestive of sleep deprivation (Woodward & Freedman, 1994).

Given the above, it was unsurprising that global sleep quality (PSQI) would be the main predictor variable in terms of the severity of impact of nocturnal hot flushes/sweats. However, based on previous research, it would have been expected to contribute more than the 11.8% of variance in this model. In fact, the combined variance from the four predictors that entered this model only contributed 18.4% of the explained variance. These results could argue that the psychosocial measures assessed in this study were not

sensitive enough to pick up model variance. More probably, they suggest that factors other than those used in this study may better predict transitional women's ratings the severity of impact of nocturnal flushes/sweats.

8.4 The Relationship Between Pineal Melatonin and Psychogenic Symptoms:

Initially 26 women agreed to participate in Study 2, designed to explore the role of melatonin in a transitional population. However, prior to commencement of melatonin sampling four women withdrew, leaving a smaller sample of 22 women. Twelve of these participants were assigned to the good psychogenic health group (lowest psychogenic frequency symptom scores) and ten were assigned to the poor psychogenic health group (highest psychogenic frequency symptom scores). Cost constraints involved in RIA testing precluded a complete 24-hour sampling design. The results reported relate only to baseline (day-time) and evening on-set of rhythms. No data is reported in relation to night-time plateau, or off-set rhythms. Total secretion levels refer only to levels obtained from 9.00 am to midnight on Day 1 of sampling and from first awakening (approximate time 7.30 am) and 10.00 am on Day 2. As previously discussed in Section 8.2, results from this study found no significant differences in melatonin secretion levels for HRT users and non-users within the good psychogenic health group. Similarly there were no significant differences reported for secretion levels for HRT users and non-users within the poor psychogenic health group. Thus the following

results are discussed in terms of psychogenic health group membership (good/poor) irrespective of method of transition (natural/HRT-assisted).

Visual inspection of melatonin secretion levels at sampling time points for individual participants' raw and standardized levels (Figures 7.1 (a) & (b), Figures 7.2 (a) &(b)) show a more even on-set of rhythm pattern for the good psychogenic health group, as opposed to a peak/trough pattern for the poor group. However, no significant difference was found between the two groups in terms of partial area under the curve (AUC) calculations, or in terms of total secretion levels during the study period. It is possible that the sample size of 22 was too small to detect such differences, should they have existed. While a Cohen's d showed a medium to large effect size for AUC, the subsequent power calculation reported only a 62% chance of detecting a significant difference at alpha =.05, should such a difference exist. Alternatively, the results may reflect those of other studies within a similar age group that also failed to report significant differences. In examining melatonin secretion levels in a mixed gender population of good sleepers and insomniacs with an average age range of 63.5 years to 66.2 years, Lushington, et al. (1998) also reported no significant difference in either 12 hour or 24 hour total melatonin secretion levels. Kripke, et al. (1998) reported similar results in their study of good and poor sleeping post-menopausal women aged between 50 to 81 years (average age 71 years).

While finding no significant differences in total secretion levels, Kripke, et al. (1998) did report a significant difference in terms of the 24 hour melatonin acrophase (peak of the cosine curve), where 42% of post-menopausal participants had acrophases outside the normal range established in a healthy young adult control group. The present study, while unable to compare 24-hour acrophases, did examine the melatonin on-set of rhythm of good and poor psychogenic health group participants. Mean secretion levels for both groups were compared at all melatonin sampling time points. Visual inspection of the resultant time sequence plots (Figure 7.4) showed that both groups had almost identical baseline levels. However, from 6.00 pm onward the secretion profile of the good psychogenic health group rose at a higher level for all time sampling points up to and including the midnight sample. A mixed design Split Plot analysis showed a trend ($\underline{p}$ = .087) toward significantly higher on-set of rhythm levels in the good psychogenic health group from 8.00 pm to midnight, with the greatest difference occurring at the 10.00 pm sampling point. This time point was established as the optimum time for the first steep rise in nocturnal melatonin secretion levels in healthy young females, with levels reaching a plateau between 2.30 am to 4.00 am (Bispink, et al., 1990). Bojkowski, et al. (1987) also reported that some 81% of 24 hour melatonin secretions in healthy adults occurred in the time period 10.00 pm to 4.00 am. Within the poor psychogenic health group, the steepest rise occurred at the 11.00 pm time

point, but levels only marginally increased from 11.00 pm to the midnight time point (see Figure 7.5). As no data with regard to overnight secretion levels was available to the present study, it is not possible to speculate on levels attained by the two groups after midnight.

The most obvious influence on melatonin levels is the light/dark cycle (Reiter, 1991). Participants in the present study wore a light monitoring device from awakening until midnight on Day 1 of melatonin sampling. Minutes of exposure to natural light were calculated at 500, 3,000 and 10,000 lux levels. Time sequence plots for the three lux levels plotted from 9.00 am to 6.00 pm (Figures 7.6 (a),(b) and (c)) show that at each lux level women in the good psychogenic health group had greater exposure to natural light than their poor group counterparts. A subsequent MANOVA found a significant difference at all lux levels in terms of exposure time, with the good psychogenic health group being exposed to significantly longer periods of light at 500, 3,000 and 10,000 lux than the poor psychogenic health group.

There has been much research interest in the role of the light/dark cycle in the entrainment of deviant melatonin rhythms, some of which has been briefly outlined in Chapter 5. Studies in this area have, in the main, involved the use of artificial light (bright light treatment) to attempt to re-entrain deviant rhythms caused by shift work (eg: Dawson, et al., 1995,

Quera-Salva, et al., 1996) or to alleviate symptoms associated with seasonal affective disorders (SADs) (eg: Lewy, 1982, Rice, et al., 1995, Partonen, et al., 1997). As this study did not use artificial light as part of its protocol, it is not possible to extrapolate the results in terms of exogenously induced bright light phasic shifts.

In terms of the effects of natural light, entrainment of the sleep/wake cycle in humans occurs via the retino-hypothalamic tract to the supra-chiasmic nucleus (SCN) (Moore & Lenn, 1972), with the cyclical rhythm of melatonin secretion synchronized by the retina's absorption of light and dark (Arendt, 1988). Total melatonin secretion levels appear to remain unaffected by shorter hours of exposure to natural light (Wetterberg, et al., 1992). However, seasonal influences can change human secretion profiles. Extended natural light during summer evenings has been shown to delay initial evening on-set of rhythm, with darker winter mornings prolonging nocturnal plateau levels (Chase & Gidal, 1997). When treating SAD sufferers with either natural light (a one hour early morning walk) or low dose artificial light (0.5 hr @ 2,500 lux), Wirz-Justice, et al. (1996) reported a melatonin phase advance in 71% of morning walkers that did not occur in the artificial light group. More recent findings in rat studies point the to involvement of the SCN in the regulation of the amplitude of melatonin rhythms. Bothorel, et al. (2002) maintained rats over a period of 4 days on a 12 hour light/12 hour

dark cycle, while subcutaneous injections of exogenous melatonin (dosage 1mg/kg) were delivered. Bothorel et al. reported a 100% increase in melatonin peak amplitude, sustained over a period of 2 days, when exogenous melatonin was subcutaneously injected at the onset of darkness. Similar results were obtained when exogenous melatonin at the same dosage rate was injected directly into the SCN, but did not occur when the dosage was injected into the pineal gland. While exploratory, Botheral et al's results could suggest that although the pineal gland controls the total secretion levels of melatonin, the amplitude of its rhythms are regulated by the SCN. If this is so, it reinforces the potentially critical role of light in changing the amplitude of melatonin rhythms. This differentiation may account for amplitudinal changes that are not mediated by corresponding changes in total secretion levels.

There is no doubt that in this study, participants who experienced infrequent psychogenic symptoms (the good health group) had significantly greater exposure to natural light on Day 1 of melatonin sampling than participants who experienced more frequent psychogenic symptoms (the poor health group). Whether this exposure led to the higher on-set of rhythms during evening on-set could not be established by this study. It could however be hypothesised that lower psychogenic symptom frequency enabled the good psychogenic health group to be more active, spending

significantly more time outdoors on the day of testing than women in the poor health group. The psychogenic symptom, lack of energy, was the third most frequently reported symptom in Study 1, with 23% of women also according it a maximum score of three in terms of major disturbance on their ability to maintain their normal lifestyle. In combination with the other psychogenic symptoms of trouble sleeping, sadness/downheartedness, difficulty in concentration and nervous tension, it is quite plausible to suggest that women within the poor psychogenic health group lacked the physical or mental energy to pursue social and recreational activities outside the house. In this context, melatonin sampling had deliberately been scheduled for a weekend, with the main day of testing being a Saturday. No data was obtained from participants with regard to employment outside the home, or in regard to the type of activity undertaken on the Saturday of sampling. Conversely, it could be hypothesized that the women within the good psychogenic health group had had a regular lifestyle that had involved more outside activity. This, in itself could have led to lower psychogenic symptoms within the group. In this context, Wirtz-Justice et al. (1996) reported a significant decrease in depressive symptoms within SAD sufferers who were exposed to natural light during regular early morning walks. When presenting research findings at the Associated Professional Sleep Societies 17th Annual Meeting in Chicago, Armitage, et al. (2003) also noted the involvement of natural light in major depressive disorders (MDD) in children

and adolescents. When comparing 59 un-medicated young MDD sufferers and 41 non-symptomatic controls, Armitage et al. reported a significant difference in amount of exposure to natural light and physical activity over five consecutive days between the two groups. The young MDD sufferers had significantly lower levels of physical activity and lower exposure to natural light (assessed at levels of >1,000 lux) than their non-symptomatic counterparts.

With regard to participant group in the present study, it appears beyond argument that the women with good psychogenic health spent considerably more time outside the house, given that domestic light intensity is assessed at approximately 500 lux (Arendt, 1988). While melatonin and light sampling took place over several weekends, it was all undertaken during the non-daylight saving period to preclude the possibility of some participants being monitored on mid-summer days of exceptional light intensity. No significant differences were found in partial AUC, possibly due to an insufficient sample size. While no significant differences were found in total melatonin secretion levels of the two groups, a trend was evident, even given the sample size, in terms of higher and earlier evening on-set of rhythm in the good psychogenic health group. The earlier and higher on-set of rhythm in the good psychogenic health group could well be linked to their greater exposure to higher levels of natural light. Whether the ability to gain this

greater exposure to natural light is due specifically to the less frequent incidence of psychogenic symptoms in the good psychogenic health group cannot be determined in this study. The results do support the argument for further research into the relationship between melatonin and the psychogenic symptoms of menopausal transition. In particular, to ascertain whether transitional women with good psychogenic health continue to maintain a higher amplitude pattern when assessed over a full 24-hour melatonin sampling schedule.

8.5 Possible Role of Exogenous Melatonin:

There is no evidence from current research to suggest that taking exogenous melatonin could result in an improved menopausal transition, or that is should be taken in any *ad hoc* way by menopausal women in the hope that it would improve their transitional symptoms. Certainly, this is an area for further research, with controlled clinical studies assessing the effects of exogenous melatonin in a transitional population. It could be argued, from the current research findings, that use of exogenous melatonin may lead to a better entrainment of evening on-set of rhythms, which could result in a decrease in the frequency of psychogenic symptoms associated with menopausal transition. However, the role played by greater exposure to natural light and the mediating effects of the psychosocial environment would suggest there is unlikely to be a simple connection between melatonin and the psychogenic symptoms of menopause.

8.5.1 Need for Caution:

The efficacy of long-term usage of exogenous melatonin is still unclear. Arnedt (1997) points out that, while melatonin shows low toxicity in acute toxicological evaluations, there is no published safety data on its long-term use. Based on 16 years experience in both laboratory and field studies, Arnedt noted no significant side effects at a dosage rate of 5 mg or less oral fast-release melatonin, used on a daily basis for a period of six months. The proviso for the above usage rate was that the user was over 18 years of age, healthy, not pregnant or lactating, had no history of personal or familial psychiatric disorders, and was un-medicated other than using oral contraceptives or mild analgesics. While readily available in the United States of America, melatonin is now available as a "health" product within the natural health market in Australia. Publications attesting to its benefits and usage are widely available over the Internet. One example is from the Review of Natural Products (2001), which recommends people having difficulty in maintaining sleep to "take a high dose, repeated low doses, or a combined release formulation" without specifying any dosage level. It is not the intent of the author to recommend that exogenous melatonin be taken outside clinical trials designed to establish its safety and efficacy for use in alleviating menopausal symptoms within a transitional population.

8.6 Quality of Sleep and Incidence of Nocturnal Hot Flushes within Good and Poor Psychogenic Health Participants:

The design for Study 2 had initially incorporated monitoring of peripheral body temperature concurrent with melatonin sampling on Days 1 and 2 of the study. Unfortunately, the only peripheral body temperature (PBT) probe recommended for use with the PDMDs available to this study proved impracticable for use in conjunction with the lux monitor. Because of this problem, no results could be obtained with regard to any association between melatonin secretion levels and/or rhythms and peripheral body temperature. However, no problems were encountered when the PBT probe was worn during sleep in conjunction with the wrist-band used to assess nocturnal sleep activity levels. This discussion section will therefore address only results obtained for the five nights of sleep and PBT monitoring.

Numerous research studies have reported a high incidence of problems with the quality of sleep, changes in sleep architecture and nocturnal hot flushing episodes within a menopausal population (see Chapter 2). This study also examined subjective and objective sleep quality, nocturnal flushing experiences and nocturnal peripheral body temperatures over five nights. The two groups compared in terms of these measures were those used in the melatonin comparison. That is, women assessed as having good psychogenic health (N=9) and women assessed as having poor psychogenic health (N=9).

No significant difference was found between the two groups in subjectively measured quality of sleep (grade of normality, sleep efficiency and sleep fragmentation), although in each measure women within the good psychogenic health group had lower mean scores indicative of better subjective sleep quality. Similarly, women in the good psychogenic health group had lower mean scores in terms of mean nocturnal activity levels and movement and fragmentation indices, and higher mean scores in terms of nocturnal immobility periods indicative of better sleep quality. However, again MANOVA analysis failed to find any significant differences between the two groups in terms of objectively assessed sleep quality.

Given the small sample size (N = 18) it is possible that there was insufficient sample power to statistically establish any significant differences between the two groups. However it is also possible that, given the selection criteria for Study 2, no statistically significant differences did exist between the two groups in terms of their subjective or objectively assessed quality of sleep. Previous research has reported significant differences in sleep quality and sleep architecture in menopausal women when compared to their pre-menopausal counterparts (Shaver & Paulsen, 1993, Baker, et al., 1996). This author's Honours thesis (Bliss, 1998) using the same sample size and same monitoring equipment did find significant differences between self-reporting good and poor menopausal sleepers in terms of both mean nocturnal activity

levels and movement indices. However, in the present study, participants were neither selected, nor assigned to good or poor psychogenic health groups on the basis of their quality of sleep *per se*, but on their accumulated psychogenic symptom frequency scores (PSF). When discussing the results from Study 1, it was noted that, in terms of predictors of impact of psychogenic symptom severity, global sleep quality (PSQI) contributed only 5.4% toward the explained total variance of 57.9%, with general psychological health (GHQ-30) being the major contributor (40% of variance). These results suggest that trouble sleeping on its own does not contribute significantly toward distinguishing good and poor levels of psychogenic health within a transitional population.

In terms of nocturnal peripheral body temperatures and self-reported incidence of nocturnal hot flushes/sweats, significant differences were found between the two groups. Participants with poor psychogenic health reported significantly more hot flush/sweat episodes during the five study nights (60 episodes over the five night monitoring period) than their good health counterparts (23 episodes). As part of the Melbourne Women's Mid-Life Health Project, Guthrie, et al. (1996) noted that the highest incidence of flushing episodes occurred in women who had achieved between three to 12 months amenorrhoea (designated as being in early transition in the present study). As the majority of women in early transition in the present study

were in the good psychogenic health group, the increased incidence of nocturnal flushes reported by the poor psychogenic health group could not be attributed to a predominance of women in early transition being poor psychogenic health group members.

Participants in the poor psychogenic health group also reported the severity of their nocturnal hot flushes/sweats as significantly more severe than did participants in the good psychogenic health group. In this latter context, these results give support to the findings of Hunter and Liao (1995) who reported psychogenic-type symptoms (depressed mood, anxiety and low self-esteem) as the main discriminators between women who saw hot flushes and night sweats as problematic and those who did not.

Independent t-tests found no significant differences in terms of psychogenic health group membership with regard to either mean 5-night minimum PBT or mean 5-night maximum PBT. However statistical analysis of mean 5-night hours spent at 35º to 36º (the highest incremental PBT range achieved by all participants) showed a significant difference between the two groups. Participants assigned to the poor psychogenic health group spent significantly more hours (mean 3.23 hours) at this PBT range than their good psychogenic health counterparts (mean 2.34 hours). In terms of the time spent at the higher PBT range, no previously published research studies have

been found that record nocturnal PBT levels within a menopausal population. Using a similar PBT probe, Freedman (1989) did graphically report dorsal finger temperatures during spontaneous diurnal hot flushes as commencing at approximately 30.5ºC and rising over a five minute period to temperatures in excess of 33ºC. It was not possible, given the study design in regard to objective sleep monitoring, to have participants record the times at which nocturnal flushes/sweats occurred. However, it is not unreasonable to suggest that the higher self-reported incidence of nocturnal hot flushes/sweats reported by the poor psychogenic health group are reflected in the significantly longer hours they spent at elevated peripheral body temperatures.

8.7 Reliability and Validity of Study Results:

Several methodological limitations are discussed below in terms of study design, equipment malfunctions and their subsequent affect on the reliability and validity of the study results.

In any community-based research project it is important to assess the degree to which the study population reflects the general population. In the present study significant efforts were made to maximise this representation. Of the 71 participants who took part in Study 1, 54% (N=38) responded to articles in local newspapers, or were friends or acquaintances of responders, while 46% (N=33) were recruited from within the various campuses of

Victoria University. A wide geographical sampling distribution can be seen from the mix of participants' Melbourne postcodes (see Appendix 8.1). While all were volunteers, none were recruited directly from menopausal clinics or other health-seeking venues. Menopausal symptoms frequency reporting was in line with that of large-scale studies that did use random selection (Massachusetts Women's Health Study, Melbourne Women's Mid-Life Health Project). HRT usage levels were similar to those reported in or extrapolated from other Australian studies.

It is acknowledged that some demographic and socio-economic details were not collected. For example, information was not requested regarding levels of education, working outside the home, current/past smoking habits, or current or past alcohol usage. However, Study 1 was not designed to investigate specific areas of menopausal transition, but to establish, in part, the predictive value of a number of psychosocial measures on the severity of impact of menopausal symptoms. Some menopausal research studies have used such data when exploring specific areas of transition. For example, smoking has primarily been linked to earlier on-set of peri-menopause (McKinlay et al., 1992) but was not a predictor of well-being or sexuality during transition (Cawood & Bancroft, 1996). Alcohol usage has been linked to hot flushes in women with either a deficiency or a low level of activity of alcohol dehydrogenase (Frishman, 1995,). However, Hunter and Liao (1995)

noted no significant association between frequency of menopausal hot flushes and alcohol use, cigarette smoking, employment or education levels in a sample of 61 mid-aged English menopausal women (mean age = 52.41, SD = 6.82 years). In terms of socio-economic status, any study using volunteers will tend to be skewed toward those in the middle or high SES categories. The present study also included 46% of participants who were recruited via the global staff and academic e-mail system of Victoria University. It is therefore acknowledged that there is a probability of many participants in the study being in the middle to high SES categories. Given the above, while the data may have been of general demographic interest its omission is not seen as affecting the reliability or validity of the results reported.

Study 2 did explore areas where alcohol usage may have affected the results. Wetterberg et al., (1992) reported an association between low total secretion levels of urinary melatonin and alcohol. However, the participants in the Wetterberg et al. study were male, recovering alcoholics who were attending medical facilities as outpatients. Citing the previous research of Murialdo, et al., (1991) Wetterberg noted that their study had shown that alcohol markedly increased the daytime melatonin secretion patterns of alcoholics. It is possible that some participants in the present study used higher than social levels of alcohol on a regular basis. However, the reporting of alcohol usage in community-based self-report sampling relies on

participants not under-estimating their daily consumption, with no reliable way of verifying such reported levels at the time of data collection. Based on the finding of Murialdo et al. an unusually high percentage of high alcohol-using participants would have expected to have been reflected in higher than normal base-line (daytime) levels of melatonin. This was not the case in the present study.

Participants were not asked to specify the type of HRT used (oestrogen only or combined oestrogen-progesterone). In line with Stephens and Ross (2002) this study sought to establish whether there were significant differences in severity of impact of menopausal symptoms between HRT and non-HRT users, and thus reported HRT-users as a single group regardless of type of preparation used. The progesterone component of combined HRT is recommended as protection against uterine cancer in transitional women with intact uteri (Cabot, 1996). The oestrogen component, linked in some studies to brain chemistry and mood (Purdie et al., 1995, Brace & McCauley, 1997, Sherwin, 2000, Boyle & Murrihy, 2001) is common to both types of HRT. Thus, the exclusion of data relating to type of HRT used is not seen to impinge on the reported results with regard to HRT use in this study.

There were a number of methodological issues in Study 2. The first of these was the relatively small sample size (N = 22) and thus the ability to

generalise the results. As previously discussed, the size of the study sample can affect its statistical ability to detect significant differences, should they exist (Cohen, 1988). However, many of the research studies cited in Chapter 5 (Pineal Melatonin – A Review of Literature) have used similar or much smaller samples when investigating the role of pineal melatonin in a human population. Some examples of these are Bispink, et al. (1990) N = 8, Dennerstein, et al. (1993) N = 12, Tzischinsky, et al. (1993) N = 29, Bartsch, et al. (1995) N = 19, Cagnacci, et al. (2001) N = 23, Cajochen, et al. (1998) N = 10, Deacon and Arendt (1995) N = 6, McIntyre and Morse (1990) N = 20, Rice, et al. (1995) N = 11, Thompson, et al. (1998) N = 22, Wirz-Justice, et al. (1996) N = 20 and Zimmerman, et al. (1993) N = 11. These small sample sizes reflect the intensive nature of these types of studies and their high cost.

The saliva samples were collected and stored in accordance with current protocols. A reliable testing assay (Buhlmann) was used, and the RIA testing was performed by an independent agency (La Trobe University). It is acknowledged that the results obtained would have been strengthened had it been possible to undertake a full 24-hour sampling schedule. This was, however, outside the financial means of the study. Given the sample size was acceptable in terms of other research studies in this area, and the sampling followed correct procedures, there is no reason to believe the

results reported should not reflect a permissive link between higher melatonin evening on-set and the lower incidence of psychogenic symptom frequency within a transitional population. It should be noted that this exploratory study was designed specifically as a naturalistic study of transitional women in their own environment. Participants were instructed not to eat, drink (other than water), smoke or brush their teeth for 20 minutes prior to each saliva sample taken between 9.00 am and midnight on the day of saliva sampling. However, they were given no instructions with regard to their posture when gently chewing each salivette insert for three to five minutes, other than to remain awake and alert until after the midnight sample. Any subsequent research may wish to take account of posture and ask participants to maintain a similar posture for a specified number of minutes prior to and during the taking of each saliva sample.

There is no doubt that women in the good psychogenic health group experienced a significantly greater amount of natural light outside the home than did their poor psychogenic health counterparts. The role of natural light in the higher melatonin secretion on-set of rhythms in transitional women with good psychogenic health (low psychogenic symptom frequencies) cannot be determined by this study. However, as discussed in Section 8.5 future research studies exploring the potential benefits of exogenous melatonin and/or exposure to natural light appear warranted in relation to the

psychogenic symptom sub-cluster of menopausal symptoms. While a number of psychometric measures were used in this research, including the Pittsburgh Sleep Quality Index, no measure was specifically used to assess participants in terms of their normal awakening time. Thus, participants in Study 2 were not delineated as to whether they believed they were 'morning' or 'evening' chronotypes. In any future study of melatonin rhythms within a similar menopausal population, the use of the Horne-Ostberg Morningness-Eveningness Questionnaire could be a useful tool to aid in excluding extreme chronotypes who may typically have different on-set and off-set times in their melatonin rhythms.

Equipment problems with the physiological data monitoring devices (PDMDs) led to the exclusion of any peripheral body temperature (PBT) data being collected concurrent with the melatonin sampling. This was due to the design of the PDMDs available to this study and the subsequently found impracticality of monitor lead connections for PBT and lux monitoring at the same time. Again, it is acknowledged that a concurrent profile of PBT and melatonin secretion on-set of rhythm levels would have been of interest. However, this study was primarily designed to explore the role of melatonin in the incidence of psychogenic symptoms. As research evidence was available to show the relationship between natural light and melatonin, a decision was made to monitor lux levels during the melatonin collection

period rather than PBT. The omission of the PBT data does not detract from the results obtained in terms of melatonin secretion on-set of rhythms and exposure to natural light.

8.8 Conclusion:

This study has combined both psychosocial and biomedical models in the belief that they should be seen as complementary in understanding menopausal transition. A greater emphasis on the biomedical model may lead to an assumption that all symptoms of menopause are hormonally-based and can be alleviated by simply taking a requisite amount of any deficient hormone in its exogenous form. Similarly the psychosocial model taken alone, can lead to a belief that the symptoms of menopausal transition can be successfully negotiated given good psychological health, a caring and supportive domestic and work environment, and a fulfilling sexual relationship. It is argued that neither position, in itself, can explain the way in which menopausal transition impacts on the lives of middle aged women. In this study the results have shown that psychosocial factors can predict the way in which women report the severity of their menopausal symptoms in terms of their impact on maintenance of a normal lifestyle. They have also shown a trend toward women with low incidence of psychogenic symptoms having higher evening on-set of melatonin secretion levels, and a significantly

greater exposure to natural light than women with a high incidence of psychogenic symptoms.

However, the author suggests that these results should not be viewed *in isolation from* each other, but *in combination with* each other. Hypothetically, it could be argued that a healthy domestic environment could lead to a lower rating of the severity of impact of psychogenic menopausal symptoms. This perception of reduced severity could be associated with a greater involvement in domestic and social activities outside the home. Pursuit of these activities could increase exposure to natural light, and thus better entrain melatonin secretion on-set of rhythm. Given the links between melatonin and psychogenic symptoms, better entrainment of melatonin secretion levels and rhythms could result in less frequent psychogenic symptoms, which in itself could result in a better domestic environment (see Figure 8.1 below). This conceptualization draws together the various findings within this thesis but any inference of causation (rather than association) requires experimental verification, preferably in research designs where key factors, such as light exposure, can be experimentally manipulated.

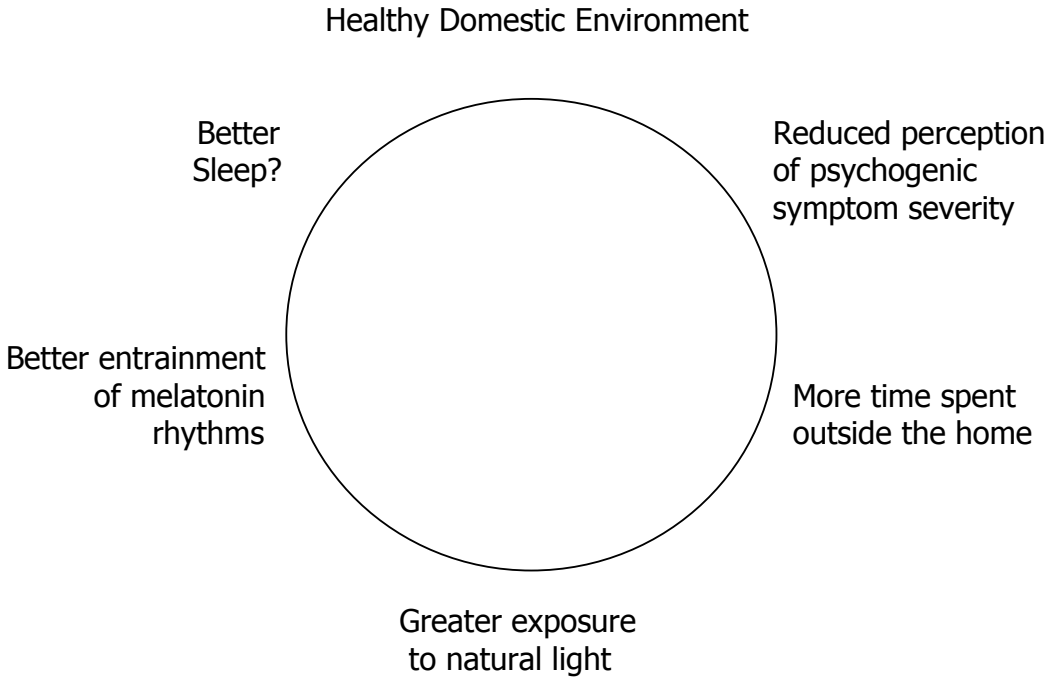

Figure 8.1: Hypothetical diagram showing the possible relationship between domestic environment, psychogenic symptoms, natural light and melatonin rhythms

REFERENCES

Abraham, S., Llewellyn-Jones, D., & Pertz, J. (995). Changes in Australian women's perception of menopause and menopausal symptoms before and after the climacteric. *Maturitas, 20* (2-3), 121-128.

Arendt, J. (1988). Melatonin. *Clinincal Endocrinology, 29,* 205-229.

Arendt, J. (1989). Melatonin: A new probe in psychiatric investigation? *British Journal of Psychiatry, 155,* 585-590.

Arendt, J. (1997). Safety of melatonin in long-term use(?). *Journal of Biological Rhythms, 12* (6), 673-681.

Armitage, R., Hoffmann, R., Emslie, T., Rintelmann, J., Moore, J., Lewis, K., & Cole, D. (2003). Rest-activity cycles in childhood and adolescent depression. *Sleep, 26* (Abstract Supplement).

Baker, A., Simpson, S., & Dawson, D. (1997). Sleep disruption and mood changes associated with the menopause. *Journal of Psychosomatic Research, 43* (4), 359-369.

Barett, J., Lack, L., & Morris, M. (1993). The sleep evoked decrease of body temperature. *Sleep, 16*, 93-99.

Bartsch, C., Seeger, H., Muck, A.O., & Lippert, T.H. (1995). The effect of estradiol on the production of melatonin in postmenopausal women. *International Journal of Clinical Pharmacology and Therapeutics, 33* (7), 401-403.

Beard, R.J. (Ed.). (1976). *The Menopause.* Lancaster, U.K.: MTP Press, Ltd.

Bellipanni, G., Bianchi, P., Pierpaoli, W., Bulian, D., & Ilyia, E. (2001). Effects of melatonin in perimenopausal and menopausal women: a randomised and placebo controlled study. *Experientia Gerontology 36* (2), 297-310.

Benedetti, F., Barbini, B., Campori, E., Fulgosi, M.C., Pontiggia, A., & Colombo, C. (2001). Sleep phase advance and lithium to sustain the antidepressant effect of total sleep deprivation in bipolar depression: new findings supporting the internal coincidence model? *Journal of Psychiatric Research, 35* (6), 323-329.

Bispink, G., Zimmermann, R., Weise, H.C., & Leidenberger, F. (1990). Influence of melatonin on the sleep-independent component of prolactin secretion. *Journal of Pineal Research, 8*, 97-106.

Bliss, R-A. (1998). A study of congruence between subjectively and objectively reported good and poor sleep in perimenopausal women. *Unpublished Honours Thesis.*

Bothorel, B., Barassin, S., Saboureau, M., Perreau, S., Vivien-Roeis, B., Malan, A., & Pevet, P. (2002). In the rat, exogenous melatonin increases the amplitude of pineal melatonin secretion by a direct action on the circadian clock. *European Journal of Neuroscience, 16* (6), 1090-1099.

Boyle G.J., & Murrihy, R. (2001). A preliminary study of hormone replacement

therapy and psychological mood states in perimenopausal women. *Psychological Reports, 88* (1), 160-170.

Brace, M., & McCauley, E. (1997). Oestrogens and psychological well-being. *Annals of Medicine 29,* 283-290.

Brambilla, D.J., McKinlay, S.M., & Johannes, C.B. (1994). Defining the perimenopause for application in epidemiologic investigations. *American Journal of Epidemiology, 140* (12), 1091-1095.

Bruck, D. (2001). The impact of narcolepsy on psychological health and role behaviours: negtive effects and comparisons with other illness groups. *Sleep Medicine, 2,* 437-446.

Brzezinski, A., Cohen, M. Ever-Hadani, P., Mordel, N., Schenker, J.G., & Laufer, N. (1994). The pattern of serum melatonin levels during ovarian stimulation for in vitro fertilization. *International Journal of Fertility, 39*, 81-85.

Brzezinski, A. (1998). Melatonin replacement therapy for postmenopausal women: is it justified? *Journal of the North American Menopause Society, 5* (1), 60-64.

Burger, H.G., Cahir, N., Robertson, D.M., Groome, N.P., Dudley, E., Green, A., & Dennerstein, L. (1998). Serum inhibins A and B fall differentially as FSH rises in perimenopausal women. *Clinical Endocrinology, 48,* 809-813.

Cabot, S. (1996). Menopause: A beginning not an end. *Australian Journal of Pharmacy, 77,* 108-117.

Cagnacci, A., Arangino, S., Angioulucci, M., Mellis, G.B., Facchinetti, F., Malmusi, S., Volpe, A. (2000). Effect of exogenous melatonin on vascular reactivity and nitric oxide in postmenopausal women: role of hormone replacement therapy. *Clinical Endocrinology, 54* (2), 261-266.

Cagnacci, A., Elliott, J.A., & Yen, S.S.C. (1992). Melatonin: A major regulator of the circadian rhythm of core temperature in humans. *Journal of Clinical Endocrinology and Metabolism, 75* (2), 447-452.

Cagnacci, A., Krauchi, K, Wirz-Justice, A., & Volpe, A. (1997). Homeostatic versus circadian effects of melatonin on core body temperature in humans. *Journal of Biological Rhythms, 12* (6), 509-517.

Cajochen, C., Krauchi, K., Danilenko, K.V., & Wirz-Justice, A. (1998). Evening administration of melatonin and bright light: interactions on the EEG during sleep and wakefulness. *Journal of Sleep Research, 7*, 145-157.

Cardinali, D.P. (1981). Melatonin: A mammalian pineal hormone. *Endocrine Reviews 2* (3), 327-346.

Cawood, E.H.H., & Bancroft, J. (1996). Steroid hormones, the menopause, sexuality and well-being of women. *Psychological Medicine, 26,* 925-936.

Chase, G.E., & Gidal, B.E. (1997). Melatonin: therapeutic use in sleep disorders. *Annals of Pharmacotherapy, 31,* 1218-1226.

Cohen, J. (1988). *Statistical Power Analysis for the Behavioural Sciences*. Hillside, New Jersey: Lawrence Erlbaum Associates.

Cole, R.J., Kripke, D.F., Gruen, W., Mullaney, D.J., & Gillen, J.C. (1992). Automatic sleep/wake identification from wrist actigraphy. *Sleep, 15* (5), 461-469.

Collins, A., & Landgren, B.M. (1997). Psychosocial factors associated with the use of hormonal replacement therapy in a longitudinal follow-up of Swedish women. *Maturitas, 28* (1), 1-9.

Cutson, T.M., Meuleman, E. (2000). Managing menopause. *American Family Physician, 61* (5), 1391-1400.

Dawson, D., Encel, N., & Lushington, K. (1995). Improving adaptation to simulated night shift: Timed exposure to bright light versus daytime melatonin adminstration. *Sleep 18* (1), 11-21.

Deacon, S., & Arendt, J. (1995). Melatonin-induced temperature suppression and its acute phase-shifting effects correlate with a dose-dependent manner in humans. *Brain Research, 688,* 77-85.

Defazio, J, Meldrum, D.R., Laufer, L., Vale, W., Rivier, J., Lu, J.K.H., & Judd, H.L. (1983). Induction of hot flashes in premenopausal women treated with a long-acting GnRH agonist. *Journal of Clinical Endocrinology and Metabolism, 56* (3), 445-448.

Defazio, J., Verheugen, C., Chetkowski, R, Nass, T., Jud, H.L., & Meldrum, D.R. (1984). The effects of naloxone on hot flases and gonadatrophin secretion in postmenopausal women. *Journal of Clinical endocrinology and Metabolism, 58* (3),578-581.

Dennerstein, L., Dudley, E., & Burger, H. (1997). Well-being and the menopausal transition. *Journal of Psychosomatic Obstetrics and Gynaecology, 18*, 95-101.

Dennerstein, L., Smith, A.M.A., & Morse, C., Burger, H., Green, A., Hopper, J., & Ryan, M. (1993). Menopausal symptoms in Australian women. *Medical Journal of Australia, 159,* 232-236.

Dennerstein, L., Smith, A.M.A., Morse, C., & Burger, H.G. (1994). Sexuality and the menopause. *Journal of Psychosomatic Obstetrics and Gynaecology, 15,* 59-66.

Drennan, M.D., Kripke, D.F., Klemfuss, H.A., & Moore, J.A. (1991). Potassium affects actigraph-identified sleep. *Sleep, 14* (4), 357-360.

Driver, H.S., Dijk, D.J., Werth, E., Biedermann, K., Borbely, A.A. (1996). Sleep and sleep electroencephalogram across the menstrual cycle in young healthy women. *Journal of Clinical Endocrinology, 81* (2), 728-735.

Erlick, Y., Takaryn, I.V., & Meldrum, D.R. (1981). Association of waking experience with menopausal hot flushes. *Journal of American Medical Association, 24* (5), 1741-1744.

Fernandez, B., Malde, J.L., Montero, A., & Acuna, D. (1990). Relationship between adenohypophyseal and steroid hormones and variations in serum and urinary melatonin levels during the ovarian cycle, periomenopause and menopause in healthy women. *Journal of Steroid Biochemistry, 35* (2), 257-262.

France, K., Schofield, M.J., & Lee, C. (1997). Patterns and correlates of hormone replacement therapy use among middle-aged Australian women. *Womens Health, 3* (2), 121-138.

Frank, S.M., Higgins, M.S., Fleisher, L.A., Sitzman, J.V., Raff, H, & Breslow, M.J. ((1997). Adrenergic, respiratory and cardiovascular effects of core cooling in humans. *American Journal of Physiology, 272* (2, Pt 2), R557-562.

Freedman, R.R. (1989). Laboratory and ambulatory monitoring of menopausal hot flashes. *Psychophysiology, 26* (5), 573-579.

Frishman, G.N. (1995). The hot flash: pathophysiology and treatment. *Rhode Island Medicine, 78* 132-134.

Garamszegi, C., Dennerstein, L., Dudley, E., Guthrie, J.R., Ryan, M., & Burger, H. (1998). Menopausal status: subjectively and objectively defined. *Journal of Psychosomatic Obstetrics and Gynaecology, 19,* 165-173.

Gonen, R., Sharf, M., & Lavie, P. (1986). The association between mid-sleep awakening episodes and hot flushes in post-menopausal women. *Journal of Psychosomatic Obstetrics and Gynaecology, 5* (2), 113-117.

Greendale, G.A., Redoussin, B.A., Hogan, P., Barnabei, V.M., Shumaker, S., Johnson, S., & Barrett-Connor, E. (1998). Symptom relief and side effects of postmenopausal hormones: results from postmenopausal estrogen/progestin intervention trial. *Obstetrics and Gynaecology 92* (6), 982-988.

Greenleaf, J.E. (1997). Exercise thermoregulation with bed rest, confinement, and immersion deconditioning. *Annals of Academic Science, 813,*, 741-750.

Guthrie, J.R., Dennerstein, L., Hopper, J.L., & Burger, H.G. (1996). Hot flushes, menstrual status, and hormone levels in a population-based sample of mid-life women. *Obstetrics and Gynaecology, 88* (3), 437-442.

Haimov, I., Laudon, M., Zisapel, N., Souroujon, M., Nof, D., Schlitner, A., Herer, P., Tzischinsky, O., & Lavie, P. (1994). Sleep disorders and melatonin rhythms in elderly people. *British Medical Journal, 309* (6948), 167.

Hajj, S.N, & Evans, W.H. (Eds.) (1993). *Clinical Postreproductive Gynaecology.* Connecticut: Appelton and Lange.

Hay, A.G., Bancroft, J., & Johnstone, E.C. (1994). Affective symptoms in women attending a menopause clinic. *British Journal of Psychiatry, 164*, 513-516.

Hogden, G.D., Goodman, A.L., O'Connor, A., & Johnson, D.K. (1977). Menopause in rhesus monkeys, a model for study of disorders in the human climacteric. *American Journal of Obstetrics and Gynaecology 127,* 581-584.

Hood, B., Bruck, D., & Kennedy, G. (2002). Light: A critical determinant of night-time sleep quality in the healthy aged. *Journal of Sleep Research, 11* (Suppl.1), 103-107.

Huerta, R., Mena, A., Malacara, J.M., de Leon, J.D. (1995). Symptoms at perimenopausal period: its association with attitudes toward sexuality, lifestyle, family function and FSH levels. *Psychoneuroendocrinology , 20* (2), 135-148.

Huerta, R., Mena, A., Malacara, J.M., de Leon, J.D. (1995). Symptoms at menopausal and premenopausal years: their relationship with insulin, glucose, cortisol, FSH, prolactin, obesity and attitudes toward sexuality. *Psychoneuroendocrinology, 20* (8), 851-864.

Hunter, M.S., & Liao, K.L-M. (1995). A psychological analysis of menopausal hot flushers. *British Journal of Clinical Psychology, 34,* 589-599.

Ito, M., Kohsaka, M., Honma, K., Fukuda, N., Honma, S., Katsuno, Y., Kawai, I., Homna, H., Moritoa, N., & Miyamoto, T. (1995). Changes in biological rhythm and sleep structure during the menstrual cycle in healthy women. *Seishin-Shinkeigaku Zasshi,* (3), 155-164. (Abstract cited only).

Kawakami, Arita, & Yoshida (1980). Loss of estrogen-induced daily surges of prolactin and gonadotrophins by SCN lesions in ovarectomy rats. *Endocrinology, 106* (4), 1087-1092.

Klein, N.A., Illingworth, P.J., Groome, N.P., McNeilly, A.S., Battaglia, D.E., & Soules, M.R. (1996). Decreased inhibin B secretion is associated with the monotropic FSH rise in older, ovulatory women: a study of serum and follicular fluid levels of dimeric inhibin A and B in spontaneous menstrual cycles. *Journal of Clinical Endocrinology and Metabolism, 81*, 2742-2745.

Kolb, B., & Whishaw, I.Q. (1996). *Fundamentals of Human Neuropsychology*. New York: W.H. Freeman and Company.

Kripke, D.F., Elliott, J.A., Youngstedt, S.D., & Smith, J.S. (1998). Melatonin: marvel or marker? *Annals of Medicine, 30,* 81-87.

Kripke, D.F., Youngerstedt, S.D., Rex, K.M., Klauber, M.R., & Elliott, J.A. (2003). Melatonin excretion with affect disorders over age 60. *Psychiatry Research, 118*, 47-54.

Kronenberg, F., & Downey, J.A. (1986). Thermoregulatory physiology of menopausal hot flashes: a review. *Canadian Journal of Physiological Pharmacology, 65,* 1312-1324.

Laakso, M.L., Porkka-Heiskanen, T., Alila, A., Stenberg. D., & Johansson, G. (1990). Correlation between salivary and serum melatonin: dependence on serum melatonin levels. *Journal of Pineal Research, 9* (1), 39-50.

Lack, L.C., & Lushington K. (1996). The rhythms of human sleep propensity and core body temperature. *Journal of Sleep Research, 5,* 1-11.

Lavie, P. (1986). Ultrashort sleep-wake schedule III: 'gates' and 'forbidden zones' for sleep. *Electroencephalography and Clinical Neurophysiology, 63,* 414-425.

Leibenluft, E., Feldman-Naim, S., Turner, E.H., Schwartz, P.J., & Wehr, T.A. (1996). Salivary and plasma measures of dim light melatonin onset (DLMO) in patients with rapid cycling bipolar disorder. *Biological Psychiatry, 40,* 731-735.

Lewy, A.J., Ahmed, S., Jackson, J-L., & Sack, R.L. (1992). Melatonin shifts in human circadian rhythms according to a phase-response curve. *Chronobiology International, 9* (5), 380-392.

Libbus, K., Baker, J.L., Osgood, J.M, Phillips, T.C., & Valentine, D.M. (1995). Persistent fatigue in well women. *Women and Health, 23* (1), 57-72.

Llewellyn-Jones, D., & Abraham, S. (1988). *Menopause.* Penguin Books: Ringwood, Australia.

Lushington, K., Lack, L., Kennaway, D.J., Rogers, N. van den Heuvel, C., & Dawson, D. (1998). 6-Sulfatoxymelatonin excretion and self-reported sleep in good sleeping controls and 55-80 year-old insomniacs. *Journal of Sleep Research, 7,* 75-83.

Matsukawa, T., Sessler, D.I., Christensen, R., Ozaki, M., & Schroeder, M. (1995). Heat flow and distribution during epidural anesthesia. *Anaesthesiology, 83* (5), 961-967.

McKinlay, S.M., Brambilla, D.J., & Posner, J.G. (1992). The normal menopause transition. *Maturitas, 14,* 103-115.

McKinlay, S.M., Jeffreys, M., & Thompson, B. (1972). An investigation of the age at onset of the menopause. Journal of Biosocial Science, 4, 161-173.

Meldrum, D.R., Defazio, J.D., Erlik, Y., Lu, J.K.H., Wolfsen, A.F., Carlson, H.E., Hershman, J.M, and Judd, H.L. (1984). Pituitary hormones during the menopausal hot flash. *Obstetrics and Gynaecology, 64* (6), 752-756.

Mendlewicz, M., Hoffmann, G., Linkowski, P., Kerkhofs, M., Goldstein, J., Van Haelst, L., L'Hermite, M., Robyn, C. Van Cauter, E., Weinberg, V., Weitzman, E.D. (1983). Chronobiology and manic depression

euroendocrine and sleep EEG parameters. *Journal of Advanced Biological Psychiatry, 11*, 128-135.

Middelkoop, H.A., van Hilten, B.J., Kramer, C.G.S., & Kamphuisen, H.A.C. (1993). Actigraphically recorded motor activity and immobility across sleep cycles and stages in healthy male subjects. *Journal of Sleep Research, 2,* 28-33.

Middelkoop, H.A., van Dam, E.M., Smilde-van-der-Doel, D.A., & van-Dijk, G. (1997). 45-hour continuous quintuple site actimetry: relations between trunk and limb movements and effects of circadian sleep-wake rhythmically. *Psychophysiology, 34* (2), 199-203.

Miles, A., & Philbrick, D.R.S. (1988). Melatonin and psychiatry. *Biological Psychiatry, 23*, 405-425.

Moore, R.Y., & Lenn, M.J. (1972). A retinohypothalamic projection in the rat. *Journal of Comparative Neurology,* 146, 1-14.

Moore-Ede, M.C., Sulzman, F.M., & Fuller, C.A. (1982). *The Clocks That Time Us.* Cambridge, Mass: Harvard University Press.

Moos, R.H., & Schaefer, J.A. (1986). *Coping with Life Crises: An Integrated Approach.* New York: Plenum Press.

Morrow, G.R., Chiarello, R.J., & Derogatis, L.R. (1978). A new scale for assessing patients' psychosocial adjustment to medical illness. *Psychological Medicine, 8*, 605-610.

Morse, C.A., Dudley, E., Guthrie, J., & Dennerstein, L. (1998). Relationships between premenstrual complaints and perimenopausal experiences. *Journal of Psychosomatic Obstetrics and Gynaecology,* 19, 182-191.

Owens, J.F., & Matthews, K.A. (1998). Sleep disturbance in healthy middle-aged women. *Maturitas, 30* (1), 41-50.

Okatani, Y., Morioka, N., & Wakatsuki, A. (2000). Changes in nocturnal melatonin secretion in periomenopausal women: correlation with endogenous estrogen concentrations. *Journal of Pineal Research, 28,* 111-118.

Ozaki, S., Uchiyama, M, Shirakawa, S, & Okawa, M. (1996). Prolonged interval from body temperature nadir to sleep offset in patients with delayed sleep phase syndrome. *Sleep, 19* (1), 36-40.

Parry, B.L., & Newton, R.P. (2001). Chronological basis of female-specific mood disorders. *Neuropsychopharmacology, 25* (95), S102-S108.

Partonen, T., Vakkurie, O., & Lonnqvist, J. (1997). Suppression of melatonin secretion by bright light in seasonally affective disorder. *Biological Psychiatry,* 42, 509-513.

Pearce, J., Hawton, K., & Blake, F. (1995). Psychological and sexual symptoms associated with the menopause and the effects of hormone replacement therapy. *British Journal of Psychiatry, 167*(2), 163-173.

Pearce, J., Hawton, K., & Blake, F. (1997). Psychological effects of Continuation versus discontinuation of hormone replacement therapy

by estrogen implants: a placebo-controlled study. *Journal of Psychosomatic Research, 42*(2), 177-186.

Polo-Kantola, P., Erkkola, R., Helenius, H., Irjala, K., & Polo, O. (1998). When does estrogen replacement therapy improve sleep quality? *American Journal of Obstetrics and Gynaecology 178* (5), 1002-1009.

Powell, B. (1977). The empty nest, employment and psychiatric symptoms in college-educated women. *Psychology of Women Quarterly,* 2, 15-23.

Purdie, D.W., Empson, J.A., Crichton, C., & Macdonald, L. (1995). Hormone replacement therapy, sleep quality and psychological well-being. *British Journal of Obstetrics and Gynaecology, 102* (9), 735-739.

Quera-Salva, M.A., Defrance, R., Claustrat, B., De Lattre, J., & Guilleminault, C. (1996). Rapid shift in sleep time and acrophase of melatonin secretion in short shift work schedules. *Sleep, 19* (7), 539-543.

Ralph, M.R., Foster, R.G., Davis, F.C., & Menaker, M. (1990). Transplanted suprachiasmic nucleus determine circadian period. *Science,* 248, 975-978.

Raven, P.H., & Johnson, G.B. (1992). *Biology*. St Louis: Mosby-Year Book Inc.

Reiter, R.J. (1980). The pineal and its hormones in the control of reproduction in mammals. *Endocrine Reviews, 1*, 109-113.

Reiter, R.J. (1991). Pineal Melatonin: Cell biology of its synthesis and of its physiological interactions. *Endocrine Reviews, 12* (2), 151-180.

Review of Natural Products. (2002). Melatonin. *Facts and Comparisons.*

Rice, J., Mayor, J., Tucker, H.A., & Bielski, R.J. (1995). Effect of light therapy on salivary melatonin in seasonal affective disorder. *Psychiatry Research, 56*, 221-228.

Roberts, J., Chambers, L.F., Blake, J., & Webber, C. (1992). Psychosocial adjustment in post-menopausal women. *The Canadian Journal of Nursing Research, 24* (2), 29-46.

Rosenthal, N.E., & Wehr, T.A. (1992). Towards understanding the mechanisms of action of light in seasonal affective disorder. *Pharmacopsychiatry, 25*, 56-60.

Rubin, R.T., Heist, E.K., McGeoy, S.S., Hanada, K., & Lesser, I.M. (1992). Neuroendocrine aspects of primary endogenous depression. *Archives of General Psychiatry, 49*, July, 558-566.

Sadeh, A., Lavie, P., Scher, A., Tirosh, E., & Epstein,R. (1991). Actigraphic home monitoring sleep-disturbed and control infants and young children: a new method for paediatric assessment of sleep-wake patterns. *Paediatrics, 87* (4), 494-499.

Sadeh, A., Sharkey, K.M., & Carskadon, M.A. (1994). Actigraphy-based sleep-wake identification: an empirical test of methodological issues. *Sleep, 17* (3), 201-207.

Saltman, D. (1994). *In Transition*, Marrickville, NSW: Choice Books.

Schleifer, L.A., Justice, A.J.H., & de Wit, H. (2002). Lack of effects of acute estradiol on mood in post-menopausal women. *Pharmacology, Biochemistry & Behaviour, 7* (1-2), 71-77.

Schmidt, H.S., & Kaebling, R. (1968). Laboratory adaptation effect on sleep patterns: a comparison of six consecutive nights. *Psychophysiology, 5* (2), 213-219.

Scragg, R.F.R. (1973). Menopause and reproductive span in rural Niugini, in *Proceedings of the Annual Symposium of the Papua New Guinea Medical Society*, Port Moresby.

Severino, S.K., & Moline, M.L. (1995). Premenstrual syndrome: identification and management. *Drugs, 49* (1), 71-82.

Shamir, E., Laudon, M., Barak, Y., Anis, Y., Rotenberg, V., Elizur, A., & Zisapel, I. (2000). Melatonin improves sleep quality of patients with chronic schizophrenia. *Journal of Clinical Psychopharmacology, 58* (11), 1049-1052.

Sharma, M., Palacious-Bois, J., Schwartz, G., Iskandar, H., Thakur, M., Quirion, R., & Nair, N.P.V. (1989). Circadian rhythms of melatonin and cortisol in aging. *Biological Psychiatry, 25*, 305-319.

Shaver, J., & Paulsen, V.M. (1993). Sleep, psychological distress, and somatic symptoms in perimenopausal women. *Family Practice Research Journal, 13* (4), 373-384.

Shaver, J., Giblin, E., Lentz, M., & Lee. K. (1988). Sleep patterns and stability in perimenopausal women. *Sleep, 11* (6), 556-561.

Shaver, J., Giblin, E., & Paulsen, V. (1991). Sleep quality subtypes in midlife women. *Sleep 14* (1), 18-23.

Sherman, B.J., Wallace, R.B, & Treloar, A.E. (1979). The menopausal transition: endocrinological and epidemiological considerations. *Journal of Biosocial Science (Supplement) 6*, 19.

Sherwin, B.B. (1996). Hormones, mood and cognitive functioning in postmenopausal women. *Obstetrics & Gynaecology, 87* (2 Supplement), 20S-26S.

Souetre, E., Pringuey, D., Salvati, E., & Robert, P. (1985). Circadian rhythms and depression. *Annals of Medical Psychology (Paris), 143* (9), 845-870. English abstract cited only.

Stewart, D.E., & Stotland, N.L. (Eds). (1993). *Psychological Aspects of Women's Health* Care, American Psychiatric Press: Washington, D.C.

Suzuki, S., Dennerstein, L., Greenwood, K.M., Armstrong, S.M., Sano, T., & Satohisa, E. (1993). Melatonin and hormonal changes in disturbed sleep during late pregnancy. *Journal of Pineal Research*, 191-198.

Swartzman, L.C., Edelberg, R., & Kemmann, E. (1990). The menopausal hot flush: symptom reports and concomitant physiological changes. *Journal of Behavioural Medicine, 13* (1), 15-30.

Taylor, J.A., Shi, J.P., & Leclair, O.U. (2001). Melatonin treatment for age-related insomnia. *Journal of Clinical Endocrinology & Metabolism, 86* (10), 4727-30.

Thompson, C., Franey, C., Arendt, J., & Checkley, S.A. (1988). A comparison of melatonin secretion in depressed patients and normal subjects. *British Journal of Psychiatry,* 152, 260-265.

Thomson, J., & Oswald, J. (1977). Effect of oestrogen on the sleep, mood and anxiety of menopausal women. *British Medical Journal, 2* (6098), 1317-1319.

Timiras, P.S. (Ed.). (1994). *Psychological Basis of Aging and Geriatrics.* (2nd Ed). Boca Raton: CRC Press.

Tuunainen, A., Kripke, D.F., Elliott, J.A., Assmus, J.D., Rex, K.M., Klauber, M.R., & Langer, R.D. (2002). Depression and endogenous melatonin in postmenopausal women. *Journal of Affective Disorders, 69*, 149-158.

Tzischinsky, O., Schlitner, A., & Lavie, P. (1993). The association between the nocturnal sleep gate and nocturnal onset of urinary 6-sulphatoxymelatonin. *Journal of Biological Rhythms, 8* (3), 199-209.

Vakkuri, O., Kivela, A., Leppaluoto, J., Valtonen, M., & Kauppila, A. (1996). Decrease in melatonin precedes follicle-stimulating hormone increase during perimenopause. *European Journal of Endocrinology,* 135, 188-192.

Van Hilten, J.J., Braat, E.A.M., van der Velde, E.A., Middelkoop, H.A.M., Kerkof, G.A., & Kamphuisen, H.A.C. (1993). Ambulatory activity monitoring during sleep: an evaluation of internight and intrasubject variability in healthy persons aged 50-98 years. *Sleep, 16* (2), 146-150.

Voordouw, B.C.G., Euser, R., Verdonk, R.E.R., Alberda, B. Th., De Jong, F.H., Drogendijk, A.C., Fauser, B.C.J.M., & Cohen, M. (1992). Melatonin and melatonin-progestin combinations alter pituitary-ovarian function in women and can inhibit ovulation. *Journal of Clinical Endocrinology and Metabolism, 74* (1), 108-117.

Von Muhlen, D.G., Kritz-Silverstein, D., & Barrett-Connor, E. (1995). A community-based study of menopause symptoms and estrogen replacement in older women. *Maturitas, 22*, 71-78.

Waldhauser, F., Weissenbacher, E., Tatzer, B., Gisnger, M., Waldhauser, M., Schemper, , H. (1988). Alterations in nocturnal serum melatonin levels in human growth and aging. *Journal of Clinical Endocrinology and Metabolism, 66,* 648-652.

Waldhauser, F., Boepple, A.A., Schemper, M., Mansfield, M.J., & Crowley, W.F., Jnr. (1991). Serum melatonin in central precocious puberty is lower than in age-matched prepubertal children. *Journal of Clinical Endocrinology and Metabolism, 73* (4), 793-796.

Waldhauser, F., Ehrhart, B., & Forster, E. (1993). Clinical aspects of the melatonin action: impact of development, aging, and puberty, involvement of melatonin in psychiatric disease and importance of neuroimmunoendocrine interaction. *Experientia, 49*, 671-681.

Watkins, E.S. (2002). Changing rationales for long-term hormone replacement therapy in America 1960-2000. *Health & History, 4* (1), 20-36.

Weaver, D.R., Rivkees, S.A., Carlson, L.L., & Reppart, S.M. (1991). Localisation of melatonin in mammalian brain. In: Klein, D.C., Moore, R.Y., Reppart, S.M. *Suprashiasmic nucleus: the mind's brain.* New York: Oxford University Press.

Weaver, D.R., Stehle, J.H., Stopa, E.G., Reppart, S.M. (1993). Melatonin receptors in human hypothalamus and pituitary: implications for circadian and reproductive responses to melatonin. *Journal of Clinical Endocrinological Metabolism, 76*, 295-301.

Wehr, T.A., Duncan, W.C., Sher, L., Aeschbach, D., Schwartz, P.J., Turner, E.H., Postolache, T.T., & Rosenthal, N.E. (2001). A circadian signal of change of season in patients with seasonal affective disorder. *Archives of General Psychiatry, 58*, 1008-1114.

Welstein, L., Dement, W.C., Redington, D., Guilleminault, C., & Mitler, M.M.,

in Guilleminault, C., and Lugaresi, E. (Eds.). (1983). *Sleep/Wake Disorders: Natural History, Epidemiology, and Long Term Evolution.* New York: Ravens Press.

Wetterberg, L., Aperia, B., Gorelick, D.A., Gwirtzman, H.E., McGuire, M.T., Serafetinides, E.A., & Yuwiler, A. (1992). Age, alcoholism and depression are associated with low levels of urinary melatonin. *Journal of Psychiatric Neuroscience, 17* (5), 215-224.

Wirz-Justice, A., Graw, P., Krauchi, K., Sarrafzadeh, J.E., Arendt, J., & Sand, L. (1996). Natural light treatment of seasonal affective disorder. *Journal of Affective Disorders, 37*, 109-120.

Woodward, S., & Freedman, R.R. (1994). The thermoregulatory effects of menopausal hot flushes on sleep. *Sleep, 17* (6), 497-501.

World Health Organisation. (1981). Research on the menopause. *WHO Technical Report Series, 670.*

Zhdanova, I.V., Cantor, M.L., Leclair, O.U., Kartashov A.I. and Wurtman, R.J. (1998). Behavioural effects of melatonin treatment in non-human primates. *Sleep Research On-Line, 1* (3), 114-118.

Zhou, J-N., Liu, R-Y., van Heerikhuize, J., Hofman, M.a., & Swaab, D.F. (2003). Alterations in the circadian rhythm of salivary melatonin begin during middle-age. *Journal of Pineal Research, 34*, 11-16.

Zimmermann, R.C., McDougle, C.J., Schumacher, M., Olcese, J., Heninger, G.R., & Price, L.H. (1993). Urinary 6-hydroxymelatonin sulfate as a measure of melatonin secretion during acute tryptophan depletion. *Psychoneuroendocrinology, 18* (8), 567-578.

Zulley, J. Wever, R., & Aschoff, J. (1981). The dependence on onset and duration of sleep on the circadian rhythm of rectal temperature. *Pflugers Archives, 391* (4), 314-318.

BOOK OF APPENDICES

CONTENTS

APPENDIX 3.1 : HEALTH SYMPTOM CHECKLIST

The following is a list of common problems that affect us all from time to time in our daily lives. During the past **TWO WEEKS** have you been bothered by any of them? If 'YES' please:

(a) Circle the appropriate symptom number
(b) Score (1) for minor irritation, (2) for some interference with your normal lifestyle, and (3) for major interference with your normal lifestyle
(c) Estimate the number of days that you experienced this problem during the past two weeks.

SYMPTOM	Symptom No.	Score	Days
Dizzy Spells	1		
Diarrhoea or Constipation	2		
Persistent Cough	3		
Feeling Sad or Downhearted	4		
Backaches	5		
Upset Stomach	6		
Headaches or Migraines	7		
Cold sweats during the day	8		
Cold sweats during the night	9		
Aches or stiff joints	10		
Shortness of breath at rest	11		
Tingling/pins & needles in hands or feet	12		
Sore throat	13		
Trouble sleeping	14		
Chest pain on exertion	15		
Loss of appetite	16		
Swelling in parts of your body	17		
Difficulty in concentrating	18		
Shortness of breath on exertion	19		
Nervous tension	20		
Problems with urine control	21		
Bladder infection problems	22		
Discomfort on passing urine	23		
Rapid heart beat (palpations)	24		
Hot flushes/sweats during the day	25		
Hot flushes/sweats during the night	26		
Dry vagina	27		
Troublesome vaginal discharge	28		
Lack of energy	29		
Dry eyes	30		
Dry nose or mouth	31		
Skin irritation (crawling/dryness)	32		
Breast soreness or tenderness	33		

Measure published: Dennerstein, Dudley, Hopper, Guthrie, & Burger (2000). A prospective population-based study of menopausal symptoms. *Obstetrics & Gynecology, 96* (3), 351-358

APPENDIX 3.2 : MENOPAUSE QUESTIONNAIRE BOOKLETS (MQB-1 and MQB-2)

MENOPAUSE QUESTIONNAIRE BOOKLET (MQB-1)

DAY 1

PLEASE COMPLETE THE FOLLOWING TODAY

(1) Research Consent Form

(2) Health Symptom Checklist

(3) Pre-Menopausal and Menopausal Information Form

(4) Pittsburgh Sleep Quality Index (PSQI)

Victoria University

Consent Form for Subjects involved in Research

INFORMATION TO PARTICIPANTS:

We would like to invite you to be a part of the first stage of a study which will look into a number of issues affecting women during their menopausal transition.

CERTIFICATION BY SUBJECT

I, **(Name in Capitals)**

of **(Address),**

(Postcode)

agree that I am voluntarily giving my consent to participate in the first stage of a study currently entitled:

> **The role of metatonin and psychosocial adjustment in psychogenic and nocturnal thermoregulatory symptoms during menopausal transition.**

conducted at Victoria University by Angela Bliss and Associate Professor Dorothy Bruck. I understand the overall purpose of the first stage of the study and have had the opportunity to have any questions answered. It has also been explained to me that my participation is entirely voluntary and I have the right to cease my involvement at any stage of this research, should I so desire. I have also been informed that I may be asked to participate in a second stage of this study, but again I have the right to refuse to participate should I so desire.

I have been informed that the information I provide will be kept confidential, and I freely consent to participation in the first stage of the above-named study.

Signed: Date-.

Any queries about your participation in this project may be directed to Angela Bliss (ph.9390 2373). If you have any queries or complaints about the way you have been treated, you may contact the Secretary, University Human Research Ethics Committee, Victoria University, PO Box 14428 MCMC, Melbourne, 8001 (telephone no. 03-9688 4710).

ID No:

HEALTH SYMPTOM CHECKLIST

The following is a list of common problems that affect us all from time to time in our daily lives. During the past **TWO WEEKS** have you been bothered by any of them? If 'YES' please:

(a) Circle the appropriate symptom number
(b) Score (1) for minor irritation, (2) for some interference with your normal lifestyle, and (3) for major interference with your normal lifestyle
(c) Estimate the number of days that you experienced this problem during the past two weeks.

SYMPTOM	Symptom No.	Score	Days
Dizzy Spells	1		
Diarrhoea or Constipation	2		
Persistent Cough	3		
Feeling Sad or Downhearted	4		
Backaches	5		
Upset Stomach	6		
Headaches or Migraines	7		
Cold sweats during the day	8		
Cold sweats during the night	9		
Aches or stiff joints	10		
Shortness of breath at rest	11		
Tingling/pins & needles in hands or feet	12		
Sore throat	13		
Trouble sleeping	14		
Chest pain on exertion	15		
Loss of appetite	16		
Swelling in parts of your body	17		
Difficulty in concentrating	18		
Shortness of breath on exertion	19		
Nervous tension	20		
Problems with urine control	21		
Bladder infection problems	22		
Discomfort on passing urine	23		
Rapid heart beat (palpations)	24		
Hot flushes/sweats during the day	25		
Hot flushes/sweats during the night	26		
Dry vagina	27		
Troublesome vaginal discharge	28		
Lack of energy	29		
Dry eyes	30		
Dry nose or mouth	31		
Skin irritation (crawling/dryness)	32		
Breast soreness or tenderness	33		

ID No:

PRE-MENOPAUSAL & MENOPAUSAL INFORMATION FORM

Note: Your answers to the following questions will be used to give an indication of your current menopausal status, and your pre-menopausal history. While you may not be able to remember exact dates of certain menopausal events, please answer as accurately as possible.

1 . Current Age: (years) (months)

2. Hormone Replacement Status: Please tick the box that best describes your current HRT Status:

   (a) Have never undergone any hormone replacement therapy
   (b) Am currently undergoing hormone replacement therapy

   If you ticked (b) for how long have you been undergoing HRT?:

   (c) Have previously undergone HRT but am not currently using HRT:

   If you ticked (c) when did you last use any form of HRT?:

3. Menopausal Status: Tick the box that best appropriates your current menopausal status:

   (a) Periods that are more frequent than normal bleed patterns:
   (b) Periods that are less frequent than normal bleed patterns:
   (c) More than 3 months but less than 12 months without a period:
   (d) More than 12 months but less than 24 months without a period:
   (e) More than 24 months without a period:

   If you ticked (e) how many months ago do you believe it is since your last period: (months)?

4. Pre-menopausal History: Looking back at your pre-menopausal history, please tick the box that best describes your normal pre-menopausal experiences-.

   (a) In general, my periods did not cause any disruption to my normal lifestyle:
   (b) While I had occasional problems, most of the time my periods did not disrupt my normal lifestyle
   (c) Most of the time my periods did disrupt my normal lifestyle

Pre-menstrual Tension: Again, looking back at your pre-menopausal history, please tick the box that best described your mood in the 4 to 5 days before your normal monthly period:

(a) In the 4 to 5 days before my period I felt **no different** than I had felt during the rest of the month:

(b) In the 4 to 5 days before my period I felt my mood was **somewhat worse** than I had felt during the rest of the month

(c) In the 4 to 5 days before my period I felt my mood was **much worse** than I had felt during the rest of the month

If you ticked **(c)** please describe how you felt during this time (eg. problems sleeping, tearfulness, tiredness, irritability, feelings of **low** self-worth, etc):

PITTSBURGH SLEEP QUALITY INDEX

The Pittsburgh Sleep Quality Index was shown in full in MQB-1. It is available for use by practitioners. Details can be accessed via the following reference:

Buysse, D.J., Reynolds, C.F., Monk,T.H., Berman, S.R., Kupfer, D.J.: The Pittsburgh Sleep Index: A New Instrument for Psychiatric Practice and Research. Pgychiatry-Research, 28:1 193-213, 1989.

MENOPAUSE QUESTIONNAIRE BOOKLET
(MQB-2)

DAY 2

PLEASE COMPLETE THE FOLLOWING TODAY

(1) The General Health Questionnaire (GHQ-30)

(2) The Psychosocial Adjustment to Illness Scale (PAIS)

GENERAL HEALTH QUESTIONNAIRE
(GHQ-30)

The General Health Questionnaire (GHQ-30) was shown in MQB-2

This measure is published by

The NFER-NELSON Publishing Company, Darville House, 2 Oxford Road East, Windsor SL4 1DF, Berks, England and may not be reproduced by any means, even within the terms of a Photocopying Licence, without the written permission of the published.

First published 1978 with copyright David Goldberg, 1978

PSYCHOSOCIAL ADJUSTMENT TO ILLNESS SCALE

(PAIS – SR)

The PAIS-SR was accompanied with the following instructions to this study's participants:

PLEASE READ BEFORE COMPLETING THE

P.A.I.S.

The PAIS looks at the role played by our relationships, home and family commitments, work habits, and social and leisure activities during major life transitions.

The PAIS was originally designed to evaluate the effect of major illness on these lifestyle areas, and therefore uses the word 'illness" in many of its questions.

While its use in this survey in **no way** suggests that menopausal transition is an illness, the PAIS has previously been used to assess the psychosocial aspects of various transitional periods, including menopausal transition.

When completing the questionnaire, please think of the term menopause, or menopausal transition, whenever the word ""illness" is used, and answer accordingly.

Please read the instructions carefully, but **DO NOT fill** in the section requiring personal details. Your participant identification number shown on that page is sufficient for the purposes of this study.

APPENDIX 4.1

Comparative rankings (highest to lowest) obtained using the Health Symptom Checklist from the present study (33-item HSC used) and the Melbourne Women's Mid-Life Health Project cross-sectional study (22-item HSC used)

Note: N/A indicates where comparative symptoms were not used on the 22-item Health Symptom Checklist reported by Dennerstein, et al., 1995.

Symptom	Ranking in this study	Ranking in MWMHP
Trouble sleeping	1	4
Hot flushes/sweats at night	2	6
Lack of energy	3	2
Aches/stiff joints	4	1
Sad/downhearted	5	9
Headaches/migraines	6	8
Hot flushes/sweats at day	7	7
Difficulty in concentration	8	10
Backaches	9	5
Skin irritation (crawling/dryness)	10	N/A
Nervous tension	11	3
Diarrhoea/constipation	12	15
Problems with urine control	13	13
Dry vagina	14	N/A
Swelling of body parts	15	12
Tingling/pins & needles in hands/feet	16	11
Dizzy spells	17	19
Breast soreness/tenderness	18	N/A
Shortness of breath on exertion	19	N/A
Rapid heart beat/palpitations	20	17
Dry eyes	21	N/A
Upset stomach	22	16
Sore throat	23	14
Persistent cough	24	18
Cold sweats at night	25	19
Chest pain on exertion	26	N/A
Dry nose or mouth	27	N/A
Loss of appetite	28	N/A
Cold sweats at day	29	20
Troublesome vaginal discharge	30	N/A
Shortness of breath at rest	31	N/A
Bladder infection problems	32	21
Discomfort in passing urine	33	22

APPENDIX 6.1: INSTRUCTION BOOKLETS FOR STUDY 2

WHAT TO DO IN STUDY TWO

SATURDAY MORNING:

- Remember to set your alarm for 8.30 am (or earlier if you want that first cup of coffee, etc). You cannot eat, drink, smoke or brush your teeth, from 8.40 am until you have taken saliva sample 1 at 9.00 am.

- Follow the instructions in Booklet 1 (page 2) for taking your first saliva sample at 9.00 am.

- After dressing, wear the light sensor and the actigraph until you go to bed at midnight (See Booklet 1 - page 1 instruction on how to wear light sensor).

- Follow the schedule in Booklet 1 (pages 3-5) for taking saliva samples during Saturday.

- After taking your midnight saliva sample, remove the light sensor and insert the wrist sensor and finger pad sensor. Attach both sensors as shown in Booklet 2 (page 1).

- Remember that if you take any extra saliva samples during the night, record the time you take the samples on the extra Night & First Awakening Sample" sheet in Booklet 1 (page 6), and put the salivette into your freezer as soon as you have taken a saliva sample.

- Take your first awakening saliva sample (sample 1 0) and record the time you took this sample on the "Extra Night & First Awakening Sample Sheet" in Booklet 1 (page 6), where it says "First Morning Sample - Sunday Morning". Take the last saliva sample (sample 11) at 10.00 am on Sunday morning.

  If you do not wake up until after 9.00 am on Sunday morning, please do not take a 'First Awakening Sample', but use Salivette Number 11 to take your 10.00 am saliva sample

- From Saturday night through to Wednesday night, wear the wrist band and temperature probe when you go to bed each night and take it off when you wake up each morning.

- Use Booklet 3 to record the times you to put your light out and attempted to go to sleep, any hot flushes you remember experiencing, and the times you finally woke each morning. **Start from Saturday morning.** Circle the number that corresponds to the type of sleep you felt you had for each night of the study period.

* **Thursday morning - breathe a sigh of relief and accept a very large "thank-you" for your participation in this research project.**

BOOKLET NO. 1

WEARING THE LIGHT SENSOR

AND TAKING

SALIVA SAMPLES

CONTENTS: **Page No**

WEARING THE LIGHT SENSOR

You only need to wear the light sensor while you are taking the saliva samples on Saturday.

1. When you have showered and dressed on Saturday morning, please attach the light sensor (using the tape provided) and the actigraph as shown in the diagram below. **Firmly press star button on actigraph to activate it – you will hear a small beep.**

2. Leave the sensor and actigraph on until you take your final saliva sample at midnight on Saturday.

3. After you have worn the light sensor on Saturday, please store it in the plastic bag provided. Please do not leave it in direct sunlight.

RIGHT-HAND SIDE SHOULDER**

Make sure the flat side is facing outwards

(Body diagram showing attachment points)

Tape onto your clothes

The actigraph can be clipped onto a belt, or your pants/skirt pocket

**** If you are left-handed you can reverse this and wear the actigraph and light sensor on your left-hand side.**

TAKING SALIVA SAMPLES:

1. **DO NOT** eat, drink (other than water) smoke, or brush your teeth for 20 minutes before each saliva sample is taken.

2. **TEN MINUTES** before taking the saliva sample, rinse your mouth out with water.

3. **TAKING A SALIVA SAMPLE:**

   (a) Ensure you have got the correctly numbered salivette (see “Saliva Taking Schedule).

   (b) Holding the salivette base firmly in one hand, wind the lid off and tip the contents into your mouth. DO NOT touch the insert with your hands.

   (c) Chew gently for about 30 seconds to activate saliva, then keep in mouth for 3 to 5 minutes. The longer the better! If you need to swallow excess saliva this is okay.

   (d) After 3 to 5 minutes, roll gently in mouth to ensure the insert is full of saliva, and carefully spit it back into the salivette.

   (e) Replace the lid and

   PLACE IN THE FREEZER COMPARTMENT OF YOUR REFIGERATOR IMMEDIATELY.

SALIVA-TAKING SCHEDULE : SATURDAY

8.40 am	**DO NOT** eat, drink (other than water) smoke or brush your teeth until after taking SAMPLE 1.
8.50 am	**RINSE** your mouth out with water.
9.00 am	**TAKE SAMPLE NO.1** then place in freezer.
	**********
11.40 am	**DO NOT** eat, drink (other than water) smoke or brush your teeth until after taking SAMPLE 2.
11.50 am	**RINSE** your mouth out with water.
12 noon	**TAKE SAMPLE NO.2** then place in freezer.
	*********
2.40 pm	**DO NOT** eat, drink (other than water) smoke or brush your teeth until after taking SAMPLE 3.
2.50 pm	RINSE your mouth out with water.
3.00 pm	**TAKE SAMPLE NO.3** then place in freezer.
	*********
5.40 pm	**DO NOT** eat, drink (other than water) smoke or brush your teeth until after taking SAMPLE 4.
5.50 pm	**RINSE** your mouth out with water.
6.00 pm	TAKE SAMPLE NO.4 then place in freezer.
	*********
7.40 pm	**DO NOT** eat, drink (other than water) smoke or brush your teeth until after taking SAMPLE 5.
7.50 pm	**RINSE** your mouth out with water.
8.00 pm	**TAKE SAMPLE NO.5** then place in freezer.

8.40 pm **DO NOT** eat, drink (other than water) smoke or brush your teeth until after taking SAMPLE 6.

8.50 pm **RINSE** your mouth out with water.

9.00 pm **TAKE SAMPLE NO.6** then place in freezer.

****

9.40 pm **DO NOT** eat, drink (other than water) smoke or brush your teeth until after taking SAMPLE 7.

9.50 pm **RINSE** your mouth out with water.

10.00 pm **TAKE SAMPLE NO.7** then place in freezer.

****

10.40 pm **DO NOT** eat, drink (other than water) smoke or brush your teeth until after taking SAMPLE 8.

10.50 pm RINSE your mouth out with water.

11.00 pm **TAKE SAMPLE NO.8** then place in freezer.

****

11.40 pm **DO NOT** eat, drink (other than water) smoke or brush your teeth until after taking SAMPLE 9.

11.50 pm **RINSE** your mouth out with water.

12 midnight **TAKE SAMPLE NO.9** then place in freezer.

****

IF YOU WAKE FOR ANY LENGTH OF TIME DURING THE NIGHT, PLEASE TAKE ADDITIONAL SAMPLES (Salivettes numbered 9a, 9b, 9c)

REMEMBER TO USE THE RED GLOW TORCH, RATHER THAN PUTTING ON YOUR BEDROOM LIGHT, AND PLACE SAMPLES IN FREEZER.

MAKE A NOTE OF THE TIME AT WHICH YOU TOOK ANY SALIVA SAMPLES AFTER 12 MIDNIGHT ON THE SHEET HEADED “EXTRA NIGHT & FIRST AWAKENING SAMPLES”

SUNDAY MORNING:

Please take a saliva sample at the time you are first fully awake (using Salivette No 10.) Note the time you take this sample on the 'Extra Night & First Awakening Sample Sheet' where it says "First morning sample - Sunday morning". Place sample in freezer.

9.40 am	**DO NOT** eat, drink (other than water) smoke or brush your teeth until after taking SAMPLE 11.
9.50 am	**RINSE** your mouth out with water.
10.00 am	**TAKE SAMPLE NO.11** then place in freezer.

IMPORTANT NOTE:

If you do not wake up until after 9.00 am on Sunday morning, **DO NOT** use Salivette 10 for a "First Awakening Sample" – just use Salivette 11 for your final 10.00am sample.

EXTRA NIGHT & FIRST AWAKENING SAMPLE SHEET

If you have woken for any length of time after your last saliva sample (Sample 9, taken at 12 midnight) please record the time/s you have taken extra samples during the night.

It is important to remember not to eat, drink or smoke before taking extra night-time saliva samples. You DO NOT need to rinse your mouth out with water and then wait 10 minutes if you are taking extra night-time samples.

Please remember to use the red-light torch and put the sample/s in your freezer straight away.

Sample 9a:

I took saliva sample 9a at: …….
(time of taking sample)

Sample 9b:

I took saliva sample 9b at: …….
(time of taking sample)

Sample 9c:

I took saliva sample 9c at: …….
(time of taking sample)

First Morning Sample – SUNDAY MORNING:

I took my first morning sample (Sample 10) at : …….
(time of taking sample)

BOOKLET 2

WEARING THE TEMPERATURE PROBE AND WRIST-BAND ACTIGRAPH

CONTENTS **Page No.**

Disconnecting the Light Sensor:

1. Carefully unclip the light sensor from **connection port 3** (red arrow).

2. Put the light sensor in the plastic bag provided. Store away from strong 1ight or heat.

Connecting the Temperature Probe and Wrist Band:

1. Clip the temperature probe (white coloured wire) into **connection port 1** (green arrow).

2. Clip the wrist band (grey coloured wire) into **connection port 4** (blue arrow).

Wearing the Temperature Probe and Wrist Band:

Before Bed Each Night (Saturday, Sunday, Monday, Tuesday, and Wednesday):

1. When you are ready to go to bed each night, take the temperature sensor from its small protective pouch.

2. Use the elastoplast to attach the temperature sensor to the outer side of the middle finger of your dominant hand (eg. if you are right-handed, your dominant hand is your right hand).

3. Remember to ensure that the sensor is protected by the gauze pad of the elastoplast and that the wire is pointing towards your finger-nail.

4. Fit the wrist-band firmly around your dominant wrist, with the wire pointing toward your fingers.

SEE ILLUSTRATION ON THE NEXT PAGE

5. Press the star on the actigraph very firmly – you should hear a small beep.

6. Return the actigraph to its black pouch.

Each Morning:

1. Carefully peel off the elastoplast and return the sensor to its protective pouch.

2. Unfasten the wrist band.

3. **Do not** leave the actigraph near a window or any other heat source when not in use.

BOOKLET 3

SLEEP QUALITY LOG

Starting from SATURDAY MORNING please use the sheets provided in this booklet to record your PREVIOUS NIGHT'S sleep quality

Please fill in BOTH pages for each night's sleep

(**Note**: Only one proforma sheet is shown in this appendix)

Please complete each MORNING of the study period

SATURDAY SUNDAY MONDAY TUESDAY WEDNESDAY THURSDAY

1. Last night I put my light out to go to sleep at _____ I finally woke at _____ (this is the time you woke and did not attempt to go back to sleep again)

2. Looking back on last night's sleep, was your sleep:

    0. A lot better than normal
    1. A little better than normal
    2. The same as normal
    3. A little worse than normal
    4. A lot worse than normal

3. Looking back to last night, how long do you believe it took you to go to sleep once you had put your light out?

    0. Less than 5 minutes
    1. 5-15 minutes
    2. 16-30 minutes
    3. 31-60 minutes
    4. More than 60 minutes

4. Looking at your answer to question 2., does it normally take you:

    0. A lot shorter time than this to go to sleep
    1. A little shorter time than this to go to sleep
    2. About the same time as this to go to sleep
    3. A little longer time than this to go to sleep
    4. A lot longer than this to go to sleep

5. How many times did you wake during last night's sleep:

    0. I did not wake during the night
    1. I woke 1 time during the night
    2. I woke 2 times during the night
    3. I woke 3 times during the night
    4. I woke more than 3 times during the night

6. This is a list of some common reasons for waking during the night. Please write against each reason the number of times you awoke because of this:

    Toilet Visit _____ Hot flush/sweat _____ Restless Bedmate _____

    Hearing Noises ____ Aches/Pains _____ Other Reasons _____

7. Once you had woken during the night, on average how long did it take you to get back to sleep:

    0. Less than 5 minutes
    1. 5-15 minutes
    2. 16-30 minutes
    3. 31-60 minutes
    4. More than 60 minutes

8. Looking at the **total** time you believe you were awake during the night, after you first went to sleep, was it:

    0. Less than 15 minutes
    1. 15-30 minutes
    2. 30-60 minutes
    3. 60-90 minutes
    4. Longer than 90 minutes

9. When you woke this morning did you feel:

    0. A lot more refreshed than normal
    1. A little more refreshed than normal
    2. No more or less refreshed than normal
    3. A little less refreshed than normal
    4. A lot less refreshed than normal

The following questions relate to any hot flushes/sweats you might have had during last night's sleep.

10. How many hot flushes/sweats do you believe you had during last night's sleep:

    0. No hot flushes/sweats
    1. One hot flush/sweat
    2. Two hot flushes/sweats
    3. Three hot flushes/sweats
    4. More than three hot flushes/sweats

11. Using the scale shown below, for each flush/sweat, please indicate by writing in the corresponding number, how severe you believed each flush to be.

    Flush Uncertain = 1 Mild = 2 Moderate = 3 Severe = 4

F1	F2	F3	F4	F5	F6
—	—	—	—	—	—

APPENDICES 7.1 AND 7.2

This data is available only in the printed editions of this thesis. For more information with regard to RIA results contact Angela Bliss on Melbourne (Australia) 9 390 2373.

APPENDIX 8.1

Melbourne Environs Postcodes Of Study Participants

3000	3046
3000	3056
3000	3056
3011	3058
3011	3070
3011	3070
3011	3070
3011	3072
3011	3073
3012	3073
3015	3078
3015	3083
3015	3102
3015	3136
3016	3174
3016	3179
3016	3207
3020	3224
3020	3337
3021	3338
3021	3340
3021	3429
3021	3429
3021	3429
3021	3431
3023	3437
3023	3437
3025	3440
3029	3441
3032	
3032	
3034	
3037	
3037	
3037	
3038	
3038	
3038	
3038	
3040	
3042	