PERIMENOPAUSAL DEPRESSION: CHARACTERISATION AND RISK

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ADDENDA

p 25, line 4: Add, “Clinically, understanding the aetiology of depression can dramatically change treatment planning (see Worsley et al., (2012) for a review). Depression that originates from, or is related to, organic factors could theoretically require different treatment approaches (both pharmacologically and therapeutically). By furthering our understanding of the causes of the depression during perimenopause, it is hoped that more targeted and effective treatment approaches can be utilised.”

p 38, insert after paragraph 1:

“For the purposes of the studies comprised in the current thesis, three groups of women were targeted for recruitment: (1) women who were currently experiencing depressive symptoms and were perimenopausal; (2) women who were not currently experiencing depressive symptoms and were perimenopausal; and (3) women who were currently experiencing depressive symptoms and were not perimenopausal.

Women were classified as depressed if they score above 13 on the Beck Depression Inventory II (BDI-II) which is indicative of mild depression. To determine perimenopausal status, the Greene Climacteric Scale (GCS) was used along with reports of a recent history of fluctuations in menstrual cycle.

Women were recruited via advertisements in university memo’s, posters and through advertisement at perimenopausal clinics and women’s health centres. A total of 141 women were recruited for the study, with 31 women excluded for not meeting the study criteria of being either depressed or perimenopausal. Due to the nature of the recruitment process and limits imposed in an effort to maintain participant confidentiality, data regarding where participants were recruited from was not collected. However, anecdotal data indicates the majority of the sample (n>100) had been recruited via university advertisements rather than through clinical avenues.”

p 52, Replace table:

Table 1. Descriptive demographic statistics of sample (N= 74)

	Perimenopausal Depressed *N (%)*	Childbearing Depressed *N (%)*	*p* [a]
Marital status			0.61
Single	5(12.5)	5(14.7)	
Married	20(50)	10(29.4)	
De Facto	3(7.5)	4(11.8)	
Boyfriend/girlfriend	2(5)	10(29.4)	
Separated/divorced	9(22.5)	5(14.7)	
Widowed	1(2.5)	0	
Children			
Yes	34(85)	11(32.4)	
No	6(15)	23(67.6)	
Employment			0.27
Not employed	3(7.5)	3(8.8)	
Casual/contract	3(7.5)	8(23.5)	
Part time	12(30)	8(23.5)	
Full time	22(55)	15(44.1)	
Income			0.70
<20,000	3(7.5)	3(8.8)	
21-40,000	3(7.5)	3(8.8)	
41-60,000	6(15)	10(29.4)	
61-80,000	9(22.5)	5(14.7)	
81-100,000	7(17.5)	6(17.6)	
>100,000	12(30)	7(20.6)	
Education			0.11
Did not complete high school	2(5)	0	
Completed high school	2(5)	6(17.6)	
Began university/TAFE	2(5)	2(5.9)	
Completed TAFE degree/diploma	2(5)	3(8.8)	
Completed university degree	6(15)	9(26.5)	
Began postgraduate degree	5(12.5)	6(17.6)	
Completed postgraduate degree	21(52.5)	8(23.5)	
HRT use			0.89
Currently taking	10(25)	9(26.5)	
Not currently taking	30(75)	25(73.5)	
Psychotropic use			0.13
Currently taking	12(30)	16(47.1)	
Not currently taking	28(70)	18(52.9)	

[a] *p* values from Chi Square tests for Goodness of fit

p 53, Table 2: Amend to specify *$p<0.05$ and **$p<0.01$.

p 53: Add at end of first sentence in line 11: “, t (74) = 0.64, p = 0.52”

p 57, end of paragraph 2: Add, “As a result of the low sample size and the lack of a third non-depressed perimenopausal group to use as a control, the impacts of age were not able to be considered in the current study. Future research would benefit from psychiatric interviewing so that the impacts of co-morbidities and treatments could be properly assessed. As it stands, the current study is not able to

differentiate how these factors may be impacting results. Additionally, possible biases related to participants self-identifying themselves for this research were not able to be assessed. Data on where women were recruited from was not collected and it is possible that this may have led to hidden biases in reporting. “

p 67, line 18: Remove duplicated reference for Worsely, R., Davis, S. R., Gavrilidis, E., Gibbs, Z., Lee, S., Burger, H., & Kulkarni, J. (2012). *Hormonal Therapies for new onset and relapsed depression during perimenopause*. Maturitas, 73(2), 127-133.

p 83, replace:

Table 1. Descriptive demographic statistics of sample (N= 76)

	Perimenopausal Depressed *N (%)*	Perimenopausal Non-depressed *N (%)*	*P*[a]
Marital status			0.49
Single	5(12.5)	1(2.8)	
Married	20(50)	24(66.7)	
De Facto	3(7.5)	4(11.1)	
Boyfriend/girlfriend	2(5)	1(2.8)	
Separated/divorced	9(22.5)	5(13.9)	
Widowed	1(2.5)	1(2.8)	
Children			0.61
Yes	34(85)	29(80.6)	
No	6(15)	7(19.4)	
Employment			0.40
Not employed	3(7.5)	5(13.9)	
Casual/contract	3(7.5)	3(8.3)	
Part time	12(30)	15(41.7)	
Full time	22(55)	13(36.1)	
Income			0.29
<20,000	3(7.5)	1(2.8)	
21-40,000	3(7.5)	0	
41-60,000	6(15)	4(11.1)	
61-80,000	9(22.5)	9(25)	
81-100,000	7(17.5)	4(11.1)	
>100,000	12(30)	18(50)	
Education			0.40
Did not complete high school	2(5)	0	
Completed high school	2(5)	5(13.9)	
Began university/TAFE	2(5)	1(2.8)	
Completed TAFE degree/diploma	2(5)	5(13.9)	
Completed university degree	6(15)	3(8.3)	
Began postgraduate degree	5(12.5)	5(13.9)	
Completed postgraduate degree	21(52.5)	17(47.2)	
HRT use			0.12
Currently taking	10(25)	4(11.1)	
Not currently taking	30(75)	32(88.9)	
Psychotropic use			0.10
Currently taking	12(30)	5(13.9)	
Not currently taking	28(70)	31(86.1)	

[a] *p* values from Chi Square tests for Goodness of fit

p 117, line 6 & 14: Substitute “6 coping styles” instead of “5 coping styles.”

p 121, para 2, line 1, 5 & 7: Substitute “6 coping styles” instead of “5 coping styles.”

p 123, end of line 1, Add: “Alternatively, the relationship between behavioural disengagement and history of depression may be related to other broader factors, such as lifestyle (active lifestyles being associated with less behavioural disengagement which offers the potential to protect against depression) or general life satisfaction (an active, satisfying lifestyle may be protective against depression).”

p 124, line 7: Add “The Brief Cope tool which was used in this study is a well validated tool of coping, however, it needs to be acknowledged that it is a screening tool and does not provide a comprehensive assessment of coping. Further research would benefit from more in depth analysis of the extent to which different styles are utilized.”

p 153, end of line 1, Add: “The small sample sizes for the reported studies means that the results of the current thesis need to be viewed cautiously, and further studies to make the conclusions statistically more secure are warranted.”

p 182, line 1: Add, ‘The candidate significantly contributed to the literature review of the published paper ‘Hormonal therapies for new onset and relapsed depression during perimenopause’. It is estimated that the candidate’s contribution was approximately 15% of the overall paper.

p 180, line 22: Remove duplicated reference for Worsely, R., Davis, S. R., Gavrilidis, E., Gibbs, Z., Lee, S., Burger, H., & Kulkarni, J. (2012). *Hormonal Therapies for new onset and relapsed depression during perimenopause.* Maturitas, 73(2), 127-133.

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Abstract

Epidemiological data has highlighted that during perimenopause, women show a significantly increased risk for developing either first-onset depressive symptoms, or a relapse of a previous mood disorder. Some researchers have even proposed that Perimenopausal Depression may be a unique form of depression that is associated with mechanisms unique to the perimenopausal transition. While debate is continuing regarding the possibility of Perimenopausal Depression as a unique depression subtype, the best evidence to date strongly supports the existence of a relationship between perimenopause and depression. The exact nature of this relationship, however, remains unclear.

With this in mind, the broad aims of this research were: (i) to explore whether the experience of adverse mood symptoms during perimenopause is different from that during childbearing years; (ii) to measure factors that are associated with increased or decreased risk of depressive symptoms during perimenopause; and (iii) to assess the role of personality characteristics in the development of depressive symptoms during perimenopause.

Three studies are reported. The first was an investigation of the symptomatic differences in mood profile between depressive symptoms during perimenopause, as compared to symptoms during the childbearing years. Based on self-report measures of symptoms, it was found that the depressive symptoms experienced during perimenopause could be differentiated from depression during the childbearing years. Specifically, it was found that during perimenopause, there were lower levels of depressive symptoms, there were lower levels of anxiety, and higher levels of anger, fatigue and sleep disturbance.

The second study looked at factors that were associated with increased depression symptoms during perimenopause. A number of factors that have previously been found to be associated with risk of depression symptoms at this time were considered to see if they contributed significantly to depression severity as measured using the Beck Depression Inventory 2 (BDI-II). Recent negative life events, a history of depression and severity of somatic symptoms were all found to be significant multivariate predictors of current severity of depressive symptoms. There was also a trend for a protective role for aerobic exercise.

The third study examined the role of coping styles in the development of depressive symptoms during perimenopause, above and beyond the variance explained by history of depression, somatic symptoms and recent life events. The coping styles of behavioural disengagement and self-blame were found to significantly predict BDI-II scores. Additionally, behavioural disengagement was found to mediate the relationship between a history of depression and current BDI-II scores in perimenopausal women. This indicates that either use of behavioural disengagement as a coping style chronically predisposes women to developing depressive symptoms or alternatively, a prior experience of a depressive disorder may increase the use of behavioural disengagement as a coping style. Further research into the timeframe of this association may be important to assess the chronicity with which behavioural disengagement increases depressive risk.

Collectively, the findings from these three studies have implications for our understanding of the concept of Perimenopausal Depression, as well as for the assessment and management of depression at this time. These results also have important implications for the conceptualisation of Perimenopausal Depression, its

assessment, and its treatment. This research provides clarification regarding which factors do and do not contribute to Perimenopausal Depression, and identifies targets for future research. These results suggest that the way Perimenopausal Depression is thought of and managed by health care professionals may require revision to ensure that women are provided with the information they need to make informed choices about risk, prevention, and management of depressive symptoms during this time.

Papers Published or Submitted During Candidature

Gibbs, Z., Lee, S & Kulkarni, J. (2012) *What factors determine whether a woman becomes depressed during the perimenopause?* Archive of Women's Mental Health. 15:323-332

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Gibbs, Z., Lee, S & Kulkarni, J. (2013) *The unique symptomatic profile of Perimenopausal Depression* Manuscript Submitted to Clinical Psychologist, 6th of May 2013.

Gibbs, Z., Lee, S & Kulkarni, J. (2013) *The role of coping styles in depression during perimenopause* Manuscript Submitted to Australian Psychologist, 4th January 2013.

Worsley, R., Davis, S., Gavrilidis, E., Gibbs, Z., Lee, S., Burger, H., & Kulkarni, J. (2012) *Hormonal therapies for new onset and relapsed depression during perimenopause*. Maturitas. 73 (2): 127–133.

Abstracts and conference presentations

Gibbs Z, Lee S, Kulkarni J (2012) Perimenopausal Depression: Predictive and risk factors for developing depression during the Perimenopausal transition. Canadian Psychological Association's 73rd Annual Convention. Halifax.

Monash University
Monash Research Graduate School
Declaration for thesis based or partially based on conjointly published or unpublished work

General Declaration

In accordance with Monash University Doctorate Regulation 17/ Doctor of Philosophy and Master of Philosophy (MPhil) regulations the following declarations are made:

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes one original paper published in a peer-reviewed journal, one accepted for publication in a peer-reviewed journal, and two unpublished manuscripts. The core theme of the thesis is the symptom profile of Perimenopausal Depression and what factors increase and decrease risk. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the candidate, working within the School of Psychology and Psychiatry under the supervision of Professor Jayashri Kulkarni and Doctor Stuart Lee. The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

In the case of Chapters 2, 3, 4 and 5, my contribution to the work involved the following:

Project design (in consultation with my supervisors); review of appropriate literature; securing ethics approval; recruitment of participants and experimental testing; conducting data analyses (in consultation with my supervisors); and drafting of papers. Supervisors provided input into completed manuscript drafts.

Thesis Chapter	Publication Title	Publication Status	Nature and extent of candidate's contribution
2	What factors determine whether a woman becomes depressed during the perimenopause?	Published	As above
3	The unique symptomatic profile of Perimenopausal Depression	Submitted	As above
4	Factors associated with depression during the perimenopausal transition	Submitted	As above
5	The role of coping styles in depression during perimenopause	Submitted	As above

I have renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis

Signed: [redacted] **Date:** 23/04/2013

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There are many people who have made this thesis possible. First, I would like to thank my supervisors Professor Jayashri Kulkarni and Doctor Stuart Lee. Their ideas, insights, reassurance and encouragement have been integral to this thesis. Additionally, I would like to thank Professor Margaret Hay, Professor Susan Rossel and Emeritus Professor Kim Ng for their advice and guidance regarding study design and the statistical analysis. Professor Ng deserves special thanks, as he has been a mentor for me throughout my undergraduate and postgraduate psychology career, helping me through many a statistical problem. I would also like to acknowledge the Monash Alfred Psychiatry Research Centre for the opportunity to work with this team and benefit from such brilliant minds.

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I would not have made it through my doctorate without the help and support of my classmates. I could not have asked for better companions on this difficult journey. I would especially like to thank Sophie Andrews for keeping me sane through the long days of data collection and analysis! Thinking about our lunch dates was sometimes the only thing that got me through the day. Additionally, Amber Fougere has provided invaluable guidance and support for the last few months of this journey and her help negotiating formatting was a godsend.

Finally, I would like to thank all the amazing teachers I have had throughout this degree. Being able to see the results of research being so artfully put into action was an inspiration.

Glossary

CNS	Central Nervous System
FSH	Follicular Stimulating Hormone
HRT	Hormone Replacement Therapy
LH	Luteinising Hormone
PMDD	Premenstrual Dysphoric Disorder
PMS	Premenstrual Syndrome
VMS	Vasomotor Symptoms

INTRODUCTION

0.1 Thesis outline

This thesis contains an investigation of the factors associated with symptoms of depression during the perimenopausal transition, as well as an exploration of differences in adverse mood symptoms at this time compared to during the childbearing years. The thesis comprises six chapters and includes one published manuscript and three manuscripts submitted for publication.

Chapter 1 provides an introduction and overview on the prevalence and causes of depression symptoms during the perimenopausal transition in women. This includes a review of the literature regarding the epidemiology, mechanisms, treatment, as well as the differences between depression at this time and in the childbearing years.

Chapter 2 reviews a broad range of risk and protective factors that have been shown to be related to whether or not a woman becomes depressed during perimenopause, including biological, social, psychological, cultural, and demographic factors.

Chapter 3 is the first of the data chapters and examines the differences in symptom profile between women experiencing symptoms of depression during perimenopause as opposed to depression symptoms during the childbearing years, in terms of subtle mood state differences.

Chapter 4 is the second of the data chapters and reports on the biopsychosocial factors found to be related to increased symptoms of depression during perimenopause in a sample of perimenopausal women. The impact of the various factors is described, and

possible causal mechanisms are discussed.

Chapter 5 extends on the findings of Chapter 4 by looking at the unique contribution of coping styles to the occurrence of Perimenopausal Depression. This paper examines which coping styles are influential after accounting for the influence of significant social or biological factors identified in Chapter 4. This will assist in providing a more holistic framework for understanding the potential causal mechanisms for increased symptoms of depression during perimenopause.

Chapter 6 is a general discussion in which the broader implications of these studies are considered. These include implications of the research findings for mental health services, for psychological and pharmacological treatment, and for future research.

0.2 Research Aims

Prior to beginning this thesis, it is helpful for the reader to understand the broad aims of this research.

0.2.1 Research Aim One

Although the theory of a distinct perimenopausal mood syndrome has existed for over 100 years, there remains a paucity of research that has examined the symptomatic differences between depression during perimenopause as compared to depression during the childbearing years. *Therefore, the first research aim was to explore whether the experience of adverse mood events during perimenopause is different those experienced during the childbearing years?* Results are reported in Chapter 3.

0.2.2 Research Aim Two

There remains much speculation in the literature about what biopsychosocial factors relate to increased symptoms of depression during perimenopause. *Therefore, the second research question asks what factors are associated with increased or decreased symptoms of depression during perimenopause.* Results are reported in Chapter 4.

0.2.3 Research Aim Three

Whilst there is a large body of research that looks at the role of biological and social factors associated with Perimenopausal Depression, the role of intrinsic personality factors as protective or risk factors has received far less research investigation. *Therefore, the third research question asks what roles do personality characteristics have in the development of symptoms of depression during perimenopause.* Results are reported in chapter 5.

CHAPTER 1 LITERATURE REVIEW

PERIMENOPAUSE: A PERIOD OF INCREASED RISK FOR DEPRESSION

1.1 Introduction

The transition to menopause has long been considered a time of psychological turmoil, despite the fact that the majority of women do not develop depression or other adverse mood symptoms during this time (McKinlay, Mckinlay, & Brambilla, 1987). This transition, known as perimenopause, is defined as the time immediately prior to menopause, beginning with endocrine, biological and clinical changes, and ending in the year after the final menstrual period (Brambilla, Mckinlay, & Johannes, 1994). Early in perimenopause, more extreme fluctuations in estradiol (the most abundant and potent estrogen) and progesterone begin to occur. As perimenopause progresses, cycles become unpredictable and decrease, resulting in longer periods of estrogen withdrawal (Morrison, Brinton, Schmidt, & Gore, 2006).

Kraepelin (1907) was the first to describe a distinct depression-like syndrome occurring during mid-life called “involutional melancholia”. This syndrome was characterised by onset in midlife and symptoms of fear, despondency, agitation, and hypochondriacal delusions. This midlife melancholia was widely accepted as a real and distinct entity and it was included in the Diagnostic and Statistical Manual (American Psychiatric Association, 1968), first and second editions. It was described as being linked to ‘endocrine changes’, thus closely linking it to menopause. Involutional Melancholia eventually fell out of favour among the psychological community when research subsequently failed to confirm its existence (Rinieris, 1982).

For as much research as there has been refuting the existence of a Perimenopausal Depression (Öztürk, Eraslan, Mete, & Özşener, 2006; Weissman, 1979), there has been equally compelling evidence that it does indeed exist (See Parry, 2008 for a review). What is known, is that during perimenopause the rate of depression amongst women rises anywhere from 2 to 14 times higher than in the premenopausal years (L. S. Cohen, Soares, Vitonis, Otto, & Harlow, 2006; E. W. Freeman, Sammel, Lin, & Nelson, 2006; Schmidt et al., 2000). Depressive symptoms during the perimenopausal transition are also seen at an approximately 40% greater rate than that seen in the general population (Timur & Sahin, 2010). There are several explanations for increased symptoms of depression during perimenopause, including biological and psychosocial models. The question remains whether something about the perimenopause, be it due to biological changes or life circumstance changes, brings about a unique form of depression, or whether it is a depression that is no different to that seen during other stages of life, but is perhaps confounded by the presence of other perimenopausal symptoms. The longevity of the concept of a depression syndrome associated with perimenopause alone warrants further investigation into this construct.

1.2 Perimenopause

Perimenopause occurs in most women during the ages of 40 to 55 years and is associated with a variety of biological and psychological changes. These include endocrine, vasomotor, cognitive, metabolic and somatic changes, in addition to changes in mood, irritability and hostility. The hormonal changes seen at this time are distinctive and unique to the perimenopausal period. In 2001 (reviewed in 2012), the Stages of Reproductive Aging Workshop (STRAW) created classification guidelines for a

woman's reproductive life cycle based on symptoms, menstrual cycle changes, and hormone changes (S. D. Harlow et al., 2012; Soules et al., 2001a).These have now become the gold standard for assessing menopausal stage and have helped create consistency amongst researchers.

1.3 Endocrine changes during perimenopause

The hormonal changes associated with perimenopause are not completely understood, mostly due to the complexity of these processes. What is known, is that early changes in menstrual bleeding patterns seen during perimenopause are associated with reproductive hormone levels, and that the changes to the hormonal milieu begin well before any symptoms occur (E. W. Freeman et al., 2005; Gracia et al., 2005). Several studies have found that the perimenopausal period has distinct endocrine characteristics, with early perimenopause characteristically being a period of high gonadotropin (Follicle Stimulating hormone (FSH) and Luteinizing hormone (LH)) levels and increased estradiol secretion, and later perimenopause is a time of high FSH levels and decreased estradiol secretion (Soules et al., 2001b). In research studies, reproductive status is often confirmed by the presence of elevated plasma gonadotropin (i.e. FSH levels in the context of low plasma estradiol levels: Rubinow, Roca, & Schmidt, 2007). In the past, it has been hypothesised that declining estrogen levels during the perimenopause lead to the symptoms that we associate with the transition, i.e. hot flushes and low mood. However, research is now indicating that the symptoms seen during perimenopause are related more to *fluctuations* in estradiol levels, rather than a decrease in estradiol levels. This is supported by the observation that symptoms peak during mid perimenopause and begin to settle once menopause, a time of severely decreased estrogen levels, is reached (E. W. Freeman, Sammel, & Liu, 2004; Schmidt,

Haq, & Rubinow, 2004).

1.4 Estrogen and the central nervous system

Estrogens are a group of steroids, named for their importance in the estrous cycle, which function as the primary female sex hormone. Like all steroid hormones, estrogens readily diffuse across the cell membrane. Once inside the cell, they bind to and activate estrogen receptors that in turn up-regulate the expression of many genes. The three major naturally occurring estrogens in women are estrone (E1), estradiol (E2), and estriol (E3) (Rubinow et al., 2007). Estradiol (E2) is the predominant form in non-pregnant females. All forms of estrogen are produced in the body from androgens through actions of enzymes. While estrogens are present in both men and women, they are usually present at significantly higher levels in women of reproductive age. Estrogens promote the development of female secondary sexual characteristics, such as breasts, and are also involved in the thickening of the endometrium and other aspects of regulating the menstrual cycle.

Estrogen has widespread actions throughout the CNS and modulates the transcription of many enzymes, as well as the receptor proteins for several neurotransmitters and neuropeptides (Ciocca & Vargas Roig, 1995). As a result, estrogen regulates almost all the activity of the neurotransmitters serotonin and acetylcholine(Lokuge, Frey, Foster, Soares, & Steiner, 2011). For example, estrogen modulates the synthesis of serotonin (L. S. Cohen & P. M. Wise, 1988), serotonin reuptake (Fink & Summer, 1996), serotonin receptor transcription (Sumner, 1995) and the response to serotonin stimulation (Matsuda, Nakano, Kanda, Iwata, & Baba, 1991). In addition to the effects on serotonin receptors, estrogen has been found to augment noradrenergic (NA) activity

by increasing NA turnover, decreasing NA reuptake and decreasing the number and sensitivity of dopamine D_2 receptors (Soares, Poitras, & Prouty, 2003). Estrogen affects widespread circuits in the human brain, including the neocortex, hypothalamus, pituitary gland, hippocampus and brain stem. These regions are known to be responsible for maintenance of many of the functions impacted by perimenopause, including sleep, hot flushes and fatigue, which are regulated through the hypothalamus, and also cognition and mood, which are regulated through the hippocampus and neocortex. Both the central serotonergic system and the estrogenic system are prominently involved in the regulation of mood and behavioural states (Rubinow, Schmidt, & Roca, 1998). Fluctuations in estrogen levels seen in perimenopause may therefore directly cause all of the observed physical and psychological symptoms through altered activation of each key areas of the brain.

1.5 Vasomotor changes during perimenopause

The most commonly associated symptoms of perimenopause are vasomotor symptoms (VMS), which refer to episodic flushing and sweating (Kronenberg, 1990). A hot flush is experienced as warmth beginning around the face and spreading to the chest, causing skin redness, diaphoresis (excessive sweating) and palpitations (Moline, Broch, Zak, & Gross, 2003). They affect about 75-85% of women during perimenopause. Most women experience them for up to one year, but up to 25% of women experience them for 5 years or longer (Moline et al., 2003). VMS have been consistently found to be related to the perimenopausal transition in both cross-sectional (Avis, Kaufert, Lock, Mckinlay, & Vass, 1993; Dennerstein et al., 1993b) and prospective studies (Hunter, 1990; McKinlay, Brambilla, & Posner, 1992) and have been linked to hormonal changes (E. W. Freeman et al., 2007). McKinlay (1992) found that incidences of hot flushes increase

during the perimenopause, peak at the time of the final menstrual period and then decline rapidly after this. In a longitudinal study by Hardy & Kuh (2002), they confirmed that VMS were found to be strongly related to changes in menopausal status with increases seen as women move through perimenopause. In a review, Kronenberg (1990) reported that VMS has been found in 11-60% of menstruating perimenopausal women. There are problems associated with VMS reporting. Namely, it is unclear what effect perceptions and expectations of VMS and menopause, as well as mood state, have on subsequent reporting. For example, women from non-Western cultures report fewer and less intense hot flushes than women in Western cultures (Lock, Kaufert, & Gilbert, 1988). Several factors have been found to influence the risk of reporting and/or experiencing VMS, including lower socio-economic status, general health and education (Kuh, Wadsworth, & Hardy, 1997; Schwingl, Hulka, & Harlow, 1994). Further research investigating the role of culture, SES expectation in the experience of VMS during perimenopause is warranted.

1.6 Cognitive changes during perimenopause

Cognitive problems are often reported in perimenopausal and recently postmenopausal women (Dennerstein, 2000). Cross-sectional studies have reported higher levels of self-reported forgetfulness in peri- as opposed to premenopausal women (Gold et al., 2000; Mitchell & Woods, 2001). However, few women view their cognitive symptoms as serious (Mitchell & Woods, 2001). The Seattle Midlife Women's Health Study (SWAN) examined changes in cognition during various stages of the menopausal transition. They found that forgetfulness was reported in 31% of participants who were premenopausal, 44% in the early perimenopausal period, 45% in the late perimenopausal period, and 42% in postmenopause (Gold et al., 2000). This indicates an

association between reported cognitive complaints and the commencement of the perimenopausal transition. Cross-sectional research has not found memory to vary according to menopausal stage (Henderson, Guthrie, Dudley, Burger, & Dennerstein, 2003). However, longitudinal research from the Melbourne Women's Midlife Health Project (MWMHP) has found that working memory and perceptual speed were superior in the early and late stages of perimenopause, as compared to women in mid-perimenopause (P. M. Meyer et al., 2003). Clinical trials have found that estrogen replacement therapies (ERT) may enhance cognition in perimenopausal women, indicating a potential hormonal aetiology for cognitive decline in the perimenopause (Sherwin, 1988). The extent of the therapeutic role ERT may have is unclear, with inconsistencies in the literature about the benefits of estrogen on cognition (Genazzani, 2007). However, both longitudinal and Randomised Controlled Trial (RCT) studies suggest that Hormone Replacement Therapies (HRT) use is associated with increased performance on tests of cognitive abilities such as verbal memory (Kampen & Sherwin, 1994), recall of proper names (Robinson, Friedman, Marcus, Tinklenberg, & Yesavage, 1994), verbal fluency and working memory (Miller, Conney, Rasgon, Fairbanks, & Small, 2002). Whilst modest for the most part, the effects of ERT can be substantial enough to be clinically meaningful (Genazzani, 2007).

1.7 Psychological changes during perimenopause

1.7.1 Mood

Based on studies from menopause clinics, mood disturbance is the most common perimenopausal symptom for which women seek treatment (Ayubi-Moak & Parry, 2002). Research on the relationship between perimenopause and depression shows

conflicting results, with some longitudinal studies showing associations between psychological symptoms and perimenopause (M. P. Freeman, Hill, & Brumbach, 2006; Schmidt, Haq, et al., 2004), and others finding no such relationship (Woods & Mitchell, 1997). Inconsistency can be attributed to methodological problems to do with diagnosis and endocrine heterogeneity, with different studies defining perimenopause by either menstrual-cycle characteristics or chronological age in which perimenopause occurs (Joffe, 2003). Such methods can be problematic, as there is variability in when the onset of perimenopause begins and ends, potentially resulting in participants being included who are not truly perimenopausal. In studies that have defined menopausal status by menstrual-cycle characteristics, it has been found that perimenopause doubles the risk for depressive symptoms compared to pre- and postmenopausal women (Avis, Brambilla, McKinlay, & Vass, 1994). However, the nature of the relationship between mood and perimenopausal symptoms is not clear, as it seems that high levels of stress, anxiety and expectations of the transition, potentially worsen the somatic symptoms of menopause (Avis & McKinlay, 1991; Barth Olofsson & Collins, 2000; Bauld & Brown, 2009).

1.7.2 Irritability and hostility

Irritability, rather than depression or anxiety, is frequently the primary presenting complaint in women with premenstrual, perinatal, and perimenopausal mood disturbances (Born & Steiner, 1999). Despite this, research on irritability in this area is lacking. This is possibly due to the lack of a concrete definition of irritability, along with its amalgamation with other constructs such as anger and hostility. Irritability, although defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) as an associated feature, or criterion for, other mental conditions can also be seen as

its own unique construct (American Psychiatric Association, 2000). It has been proposed that irritability might be an independent mood disorder and not merely a symptom of other mood disorders (Snaith & Taylor, 1985). Snaith & Taylor (1985) defined irritability as:

> 'A feeling state characterized by reduced control over temper which usually results in irascible verbal or behavioural outbursts, although the mood may be present without observed manifestation. It may be experienced as brief episodes, or it may be prolonged and generalized. The experience of irritability is always unpleasant for the individual and overt manifestation lacks the cathartic effect of justified outbursts of anger'.

In the past decades, there has been an increase in research on irritability, aggression and anger, with a focus on possible underlying neurotransmitter functioning (Born & Steiner, 1999). The relationship between impulsive aggression and CNS serotonin system function has been an area of particular interest and there has found to be an inverse association between overall CNS serotonin activity and 'irritable' impulsive aggressive behaviour (Bond & Cleare, 1997; Coccaro, 1989). Further evidence supporting the relationship between serotonin and irritability, selective serotonin reuptake inhibitors (SSRIs) have been found to be efficacious in reducing irritability and anger with *or without* concurrent depression (Fava, 2000; Fava, Alpert, Nierenberg, Ghaemi, & et al., 1996; Fava, Anderson, & Rosenbaum, 1990; Fava, Rosenbaum, Pava, McCarthy, & et al., 1993).

The relationship between irritability and perimenopause remains unclear, in much the

same way as the relationship between depression and perimenopause is unclear. In an observational study, Spyropoulou et al (2009) found a significant correlation between FSH and LH levels and outward irritability. There was no relationship found between VMS, insomnia and menopausal status, indicating that irritability is not a secondary product of these symptoms.

There is evidence that irritability increases during perimenopause (Bromberger et al., 2003; E. W. Freeman, Sammel, Lin, Gracia, & Kapoor, 2008) and this is consistent with anecdotal reports (Worsley et al., 2012). A study by (Kornstein et al., 2010) found that irritability was increased in premenopausal women experiencing depression, as compared to depressed women peri and postmenopause. This lack of clarity around irritability during perimenopause warrants further investigation.

1.8 Perimenopausal Depression - Incidence

Whilst there is little agreement over possible causes of higher rates of depression in midlife women, most research supports that it is a real phenomenon. Several longitudinal studies have shown increases in depressive symptoms during the perimenopausal period specifically. Freeman, Sammel, Lin, & Nelson (2006) found that participants in the Penn Study of Ovarian Aging were more than four times more likely to have high Centre for Epidemiologic Studies Depression scale (CES-D) scores (>16) compared with their scores before they entered perimenopause. Similarly, Cohen, Soares, Vitonis, Otto, & Harlow (2006), found that women with no history of major depression who experienced hot flushes associated with the perimenopause were significantly more likely to become depressed than women who had not entered perimenopause. Other community-based studies have found that depressive symptoms

in midlife women were associated not with perimenopause, but with factors such as stress, relationship problems, or somatic symptoms of perimenopause (e.g. sleep deprivation: Avis et al., 1994; McKinlay et al., 1987; Mitchell & Woods, 1996). However, more recent epidemiologic studies have found an increase in depressive symptoms in perimenopausal women compared with premenopausal women (Bromberger et al., 2003; Bromberger et al., 2011; Bromberger et al., 2001). Freeman, Sammel & Liu (2004) found that women in perimenopause were up to three times more likely to report depressive symptoms than were premenopausal women. Similarly, a history of major depression has been found to increase the likelihood of developing depression in perimenopause (Bernard L. Harlow, Wise, Otto, Soares, & Cohen, 2003; Tam, Stucky, Hanson, & Parry, 1999), however there is also an increased risk for first onset depression during perimenopause (E. W. Freeman et al., 2006). In a longitudinal study of premenopausal women with no history of depressive symptoms, Schmidt, Haq, & Rubinow (2004) found that the incidence of minor depressive episodes increased in the later perimenopausal period, as opposed to early in the transition.

1.9 Theories of Perimenopausal Depression

1.9.1 Hormonal disruption

The estrogen withdrawal theory states that depression seen during perimenopause is a result of reproductive hormone changes. The co-occurrence of this spike in depression and the changes to reproductive hormones intuitively suggests that an endocrine mechanism is involved in the pathophysiology of Perimenopausal Depression (Parry, 2008). For example, Schmidt et al. (2004) found that during the 24 months surrounding the final menstrual cycle, women were 14 times more likely to develop depression than

in the proceeding 31 years. Freeman and colleagues (2004) found an increased risk for severe depression during the perimenopause compared with premenopause or postmenopause, independent of variables such as past history of depression, VMS and sleep. Whilst the declining levels of estrogen were initially blamed for Perimenopausal Depression, estrogen levels actually increase during the early perimenopausal period, before dropping again (Burger, Dudley, & Hopper, 1999). This indicates that it is the *fluctuations* in reproductive hormones that might actually be responsible. Additionally, there is evidence that testosterone levels may impact mood during perimenopause. In a longitudinal study, Bromberger et al. (2010) found that higher levels of testosterone were associated with increased incidence of depression. There are several arguments supporting an endocrine origin of Perimenopausal Depression. These include: the co-occurrence of other menstrual cycle related mood disorders and perimenopause, the therapeutic effects of estrogen replacement therapies on Perimenopausal Depression, and the disparity in gender rates of depression across the lifespan.

There is a strong argument that an underlying susceptibility to endocrine changes is responsible for the three main reproductive hormone-related mood disorders. These are premenstrual dysphoria, postpartum depression and Perimenopausal Depression. Community and clinic-based studies have shown that premenstrual syndrome (PMS), Premenstrual dysphoric disorder (PMDD) and postnatal depression are risk factors for subsequent Perimenopausal Depression (Dennerstein et al., 1993b; Bernard L Harlow, Cohen, Otto, Spiegelman, & Cramer, 1999; Stewart & Boydell, 1993). PMS has been identified as both an antecedent as well as a frequent accompaniment to Perimenopausal Depression, leading to speculation that there is a tendency for some women to be at risk for mood destabilisation during periods of reproductive endocrine change (Richards,

Rubinow, Daly, & Schmidt, 2006).

The nature of menstrual cycle related mood disorders also points to a common cause. PMDD, which has been clearly associated with the fall in plasma estrogen levels towards the end of the menstrual cycle and resolves with the rise in estrogen levels during menses, is characterised by depression, anxiety, changes to sleep and concentration (Payne, 2003) – the same symptoms described during Perimenopausal Depression. Research has observed a higher-than-expected rate of PMS history in perimenopausal depressed women (Richards et al., 2006). However, Schmidt and colleagues (2004) were unable to identify an association between either PMS or postnatal depression with Perimenopausal Depression. An acknowledged problem in the literature is that many studies use retrospective self-reports of PMS, with many of these women, on closer inspection, not meeting criteria for PMS. The unreliability of participant self-report was highlighted by Richards et al. (2006), who found that upon investigation, the actual rate of premenstrual dysphoria was not predicted by self-reports.

Another source of evidence for the role of estrogen fluctuations in Perimenopausal Depression comes from the efficacy of hormone replacement therapies (HRT) on mood symptoms. Several studies examining the antidepressant effect of estrogen replacement in perimenopausal women have demonstrated a therapeutic effect (Joffe & Cohen, 1998; Schmidt et al., 2000; Soares, Almeida, Joffe, & Cohen, 2001). Interestingly, this finding has been found to be limited to peri- and not postmenopausal depression, indicating that treatment of fluctuations in estrogen levels, rather than overall levels, may be important for the antidepressant effects of estrogen (L. S. Cohen et al., 2003; Rasgon et al., 2002;

Schmidt et al., 2000; Soares et al., 2001). In a double-blind randomised study, Schmidt et al (2000) examined the efficacy of estrogen in the treatment of depression in perimenopausal women with and without hot flushes. A full or partial therapeutic response was seen in 80% of subjects receiving estradiol and 22% of those receiving placebo, indicating that estradiol replacement effectively treats Perimenopausal Depression independent of its effects on vasomotor symptoms (Schmidt et al., 2000).

A third line of evidence comes from the gender disparity in rates of depression. Unipolar major depression is nearly twice as common in women as it is in men (Kessler et al., 1994; Kessler, McGonagle, Swartz, Blazer, & Nelson, 1993). The pattern of depression across the lifespan further indicates a role for estrogen, with the gender disparity beginning in adolescence, at a time when puberty begins and hormonal changes begin to differentiate the sexes, and then peaking during the perimenopausal years, and levelling out postmenopause (Kessler et al., 1994). The perimenopausal period, with its associated hormonal fluctuations, but not the postmenopausal period in which hormone levels have stabilised, appears to be a period of increased risk for mood disorders. Thus it seems intuitive that at least some mood disorders have a hormone-related trigger.

1.9.1.1 Past history of mood disorders

Women who develop psychiatric symptoms in midlife are more likely to have a psychiatric vulnerability (i.e. personal or family history or psychiatric disorders). In fact, over half of women with Perimenopausal Depression have experienced a previous depressive disorder. In a longitudinal study, Avis and colleagues (1994) found that prior depression was the most predictive variable for subsequent depression in women aged

45-55 years. Depressed mood during perimenopause is particularly related to the previous experience of depressive symptoms associated with the menstrual cycle, such as premenstrual syndrome and postpartum depression(Stewart & Boydell, 1993). In several studies conducted by Freeman et al., premenstrual syndrome has been fund to be a predictor of perimenopausal symptoms (E. W. Freeman, Sammel, & Liu, 2004; E. W. Freeman, Sammel, Rinaudo, & Sheng, 2004). The evidence suggests that the perimenopause increases susceptibility to symptoms of depression, especially in women with a lifelong vulnerability. In particular, there seems to be a subset of women who have a sensitivity to changing hormone levels associated with the menstrual cycle and these women are most vulnerable at times of intense endocrine change, specifically premenstrual, postnatal and perimenopausal.

1.9.2 Vasomotor symptoms and the domino theory

It has been theorised that depression during the perimenopause may be secondary to the sleep disruption caused by hot flushes and night sweats, a concept known as *the domino theory (Schiff, Regestein, Tulchinsky, & Ryan, 1979)*. Constant mild sleep deprivation would explain the decrease in mood and increase in irritability and hostility that is seen during perimenopause. In this theory, the ability of estrogen replacement therapies (ERT) to improve mood is through alleviation of nocturnal hot flushes, resulting in an improvement in sleep (Schmidt & Rubinow, 1991).

Although not a uniform accompaniment, hot flushes are frequently associated with Perimenopausal Depression (Bromberger et al., 2010; S. D. Reed et al., 2009; Schmidt, Haq, et al., 2004; Seritan et al., 2010). Hot flushes have been shown to occur in over 80% of perimenopausal women with depression, compared to only 49% of

perimenopausal women without depression (Joffe et al., 2002). The constant mild sleep deprivation that results from these VMS could explain the decrease in mood and increase in irritability and hostility that is seen during perimenopause. Sleep disruption during perimenopause is ubiquitous, with reports ranging from 44% to 61% of perimenopausal women reporting insomnia, compared to 33-36% of premenopausal women (Brugge, Kripke, Ancoli-Israel, & Garfinkel, 1989; Moline et al., 2003) and one of the primary reasons for disturbed sleep at this time is through nocturnal hot flushes (Moline et al., 2003).

,For the domino theory to work, it would be expected that the onset of VMS would predate any mood symptoms (Rubinow et al., 2007). Instead, hot flushes and perimenopause have been found to be *independent* risk factors for depression (E. W. Freeman, Sammel, & Liu, 2004), reducing the likelihood that VMS predates all mood symptoms. Further questioning the role of VMS in depression, Bromberger (2009) found that life stress and history of psychological symptoms were more important than VMS when predicting first lifetime episodes of major depression in midlife women. IN another study, Bromberger & colleagues (2011) found that VMS were not a significant predictor of first onset Major depression in midlife women. Their findings did, however, suggest that women who have a more symptomatic perimenopausal transition are at higher risk of a major depressive episode. In a longitudinal study by Hardy & Kuh (2002), it was found that VMS symptoms are strongly related to perimenopausal status, while psychological symptoms were more strongly related to current life stresses than perimenopause status. It has also been shown that whilst VMS may be associated with depression, they are not able to account for the increased rate of depression (Bromberger et al., 2011). Further, it has been suggested that VMS can be influenced by depression.

In an observational study assessing the relationship between climacteric symptoms and psycho-social factors, Binfa and colleagues (2004) found that vasomotor and physical symptoms of the climacteric were related to perimenopause, whereas psychological symptoms were more influenced by psycho-social factors (mainly negative life events). This suggests that the relationship between VMS and psychosocial factors is limited. Overall, research indicates that there is often a co-occurrence of VMS and depressive symptoms during perimenopause. However, based on the independent impact of VMS and perimenopause on depression rates, and the inconsistency of research finding a relationship between VMS and depression, it seems the co-occurrence of VMS and depression is likely to reflect a common underlying endocrine sensitivity, rather than a causal relationship between the two. Further research to clarify this relationship is needed.

1.9.3 Psychosocial models

A relationship between stressful life events and incidence of depression has been well documented in the literature (S. Cohen, 1987; Hecht & Mensh, 1975). Some studies have suggested that perimenopausal years, and midlife more generally, is associated with significantly more stressful life events than other stages of a woman's life (Schmidt, Murphy, Haq, Rubinow, & Danaceau, 2004). In 1980, Greene and Cook found that perimenopausal women reported more negative life events than younger women. This observed increase in negative life events predominantly related to events associated with interpersonal losses (e.g., children leaving the home, death of parents). This observation forms the basis of the *empty nest* construct, which refers to the grief parents feel when their children move out of home. Several studies have found that the presence of negative life events is associated with perimenopausal mood and behaviour

symptoms (Bromberger et al., 2010; Dennerstein, Lehert, Dudley, & Guthrie, 2001; Greene & Cooke, 1980), with an increased frequency of negative events reported by women during the early perimenopause (Cooke & Greene, 1981; Greene, 1983; Greene & Cooke, 1980). Based on this observation, it has been postulated that Perimenopausal Depression occurs secondary to an increase in negative life events (Cooke & Greene, 1981; Greene, 1983; Greene & Cooke, 1980).

Rather than being perceived entirely negatively, however, it has been found that events associated with the empty nest construct are actually looked forward to (Barber, 1989). Historically, a woman's predominant role was to care for their family's needs and when children left home this resulted in a negative reaction. However, there have been considerable social changes over the last century in women's roles (Dennerstein, Dudley, & Guthrie, 2002). In a longitudinal study, Dennerstein et al., (2002) found that, for the majority of women, the departure of the last child from the home was associated with positive changes to mood state and a reduction in daily hassles. Another important social change is that the average age of women when they have their first child is increasing steadily, with 1 in 10 first time mothers being over 35 years of age (AIHW, 2003). Whilst in the past, perimenopause and departure of the first child used to coincide, we are now finding that women enter perimenopause when their children are still quite young (early to mid-adolescence). In addition, adult children are delaying leaving the family home, and are more often than not, returning after they have left. In 2006–07, 31% of people aged 20–34 years had left their parents' home and returned at some point to again live with their parents (Australian Bureau of Statistics, 2009). What this all amounts to, is that the peak in depression in mid-life no longer coincides with an 'empty nest'.

Dennerstein, Lehert, Dudley & Guthrie, (2001) found that events associated with the empty nest construct were not isolated to midlife, nor were they necessarily associated with negative mood. It has been suggested that perimenopausal depressed women can be distinguished from non-depressed women by their greater vulnerability to the negative effect of life events on self-esteem (Greene, 1983; Veeninga & Kraaimaat, 1989). It may be that the difference between perimenopausal depressed women and non-depressed women is in the way that they perceive life events. Ballinger (1985) found that depressed perimenopausal women experienced a more negative impact of life events and more feelings of being stressed than a group of asymptomatic controls. Both the presence of negative life events as well as how negatively they are viewed may therefore be more important for predicting depression risk.

There is still an argument that during midlife, women experience more personal changes and/or life events than at any other point in the lifespan (McKinlay et al., 1987). These experiences range from increased risk of illness or death of spouse, divorce or separation, unemployment, death of parents, and loss of social support (McKinlay et al., 1987). In a study by Woods & Mitchell (1997), it was found that a stressful life context was the most influential factor in accounting for depressed mood during midlife, with the perimenopausal transition offering little explanatory power. Harlow and colleagues (1999) found that, relative to married women, women who have never been married or were divorced, widowed or separated were at a significantly higher risk of depression during perimenopause. Bromberger et al. (2010) similarly found that lower levels of social support were associated with higher levels of depression. The need for women to redefine their roles, not just as mothers, but also as wives, as daughters, and as

productive women, is prevalent during the perimenopausal years. It may be that those women who do not possess robust coping strategies, or those women without external purpose in their lives, are vulnerable during this time.

1.10 Symptomatology

Clinically, the depression often seen during perimenopause is thought to be symptomatically different from depression at other stages of a woman's life (Schmidt, Roca et al. 1997). Perimenopausal Depression is anecdotally described in the literature as a dysphoric mood, characterised by feeling "blue" or depressed, irritable or "grouchy", tense or nervous (Bromberger et al., 2003). Compared to premenopausal depression, Perimenopausal Depression has increased levels of irritability and hostility (Bromberger et al., 2003; E. W. Freeman et al., 2008), increased mood lability (Holte & Mikkelsen, 1991) and anhedonia (Ozturk, Eraslan, Mete, & Ozsener, 2006) and is characterised by a more dysphoric presentation, rather than a major depressive episode (Dennerstein et al., 1993b). In an observational study, Öztürk (2006) found that pre-menopausal women who were depressed had higher levels of anhedonia than those women with Perimenopausal Depression. Worsley et al (2012) described the clinical presentation of Perimenopausal Depression as an 'on-off' phenomenon with episodes of sadness or irritability lasting for minutes to hours before spontaneously resolving. The exact nature of the relationship between irritability and perimenopause is unclear, however, with results from Kornstein et al. (2010) showing that irritability is actually more pronounced during depression premenopause. The syndrome that is described is different from the description one would expect of a major depressive episode, or even of straight dysphoria. Yet there is a paucity of research that seeks to categorically

pinpoint these differences.

1.11 Treatment

Given the morbidity associated with mood disorders, the appropriate management of Perimenopausal Depression is critical. Whilst HRT has been the standard treatment for perimenopausal symptoms in the past, reports on HRT by the Women's Health Initiative (WHI) have changed the risk-benefit ratio for HRT use. In addition to alleviating VMS, HRT use was previously recommended for prevention of cardiovascular disease and osteoporosis (Rossouw, 2002). The WHI found that long-term HRT use was associated with increased cardiovascular risk and breast cancer risks and only minimally enhanced quality of life. The indicated use of HRT is now only for short-term use in order to avoid these risk factors, with many women who are identified as being at high risk for either breast cancer or cardiovascular disease unable to use the treatment at all (Rossouw, 2002). In response to these treatment limitations for standard HRT use, new trends in treatment of Perimenopausal Depression have emerged. When considering how to treat Perimenopausal Depression, it is important to consider the severity of the depression as well as whether or not it is the first onset.

1.11.1 Hormone Replacement therapies

Estrogen therapy appears to be an effective treatment for depressive symptoms during perimenopause (See Worsley et al., 2012 for a review). Although results have been mixed, there are currently at least two placebo-controlled trials that have found that estrogen replacement therapy (ERT) is significantly more effective than placebo in treating depressive disorders in perimenopausal women, with response rates of 68-80% in the treatment groups compared to 20-22% in placebo groups (Schmidt et al., 2000;

Soares et al., 2001). They also found that treatment effect did not differ as a result of VMS, indicating the ERT has mood-enhancing effects independent of its effects on VMS (Schmidt et al., 2000). Kornstein et al. (2010) found that perimenopausal depressed women on HRT's experience fewer physical symptoms, lower levels of melancholia, and decreased sympathetic arousal. As mentioned previously, the therapeutic effects of ERT that are seen in perimenopausal women are not seen in postmenopausal women when estrogen levels are at their lowest (L. S. Cohen et al., 2003). However, this effect has not been consistently observed and it has been suggested that it is not the overall levels of circulating estrogen but rather fluctuations in these levels that are causing the mood disturbances (E. W. Freeman et al., 2006). In addition, it seems that the *balance* of their hormones, such as testosterone and progesterone, also has a significant effect on mood. Traditional HRT therapies are non-selective in their actions, resulting in unwanted side-effects such as well as endometrial and breast changes (Collaborative Group on Hormonal Factors in Breast Cancer, 1997; Writing Group for the Women's Health Initiative Investigators, 2002). This, in combination with the associated risk factors, means that HRT's are not an appealing or viable option to many women suffering from the symptoms of perimenopause.

1.11.2 Selective Serotonin Reuptake Inhibitors

After the WHI published its results concerning the risk of extended HRT use, there was a significant drop in HRT prescriptions and a concurrent rise in Selective Serotonin Reuptake Inhibitors (SSRI), a more conventional treatment for depressive symptoms (McIntyre, Konarski, & Grigoriadis, 2005). To date, there has not been much research into the efficacy of SSRI's for treatment of psychological symptoms during perimenopause. However, several clinical trials have found differences in the way pre-

and post-menopausal women respond to SSRI's (Kornstein et al., 2000), as well as differences between younger and older women (Cassano, Soares, & Cusin, 2005), with younger pre-menopausal women responding better to treatment. Comparisons between SSRI and HRT treatments have indicated similar efficacy between them (Soares et al., 2006), with some SSRI treatments showing improvement in menopausal symptoms generally (i.e., VMS), and not just in mood (Joffe et al., 2007; Soares, Poitras, Prouty, et al., 2003).

1.11.3 new generation hormone replacement therapies

The risks associated with traditional HRT's are concerning for some women, despite their efficacy. Tibolone is a newer and selective HRT that has a global estrogenic effect, with predominantly progestogenic effects in the endometrium (Swegle & Kelly, 2004). This particular HRT is able to alleviate menopausal vasomotor symptoms without stimulating the endometrium (Swegle & Kelly, 2004). Tibolone also increases circulating testosterone, which can enhance mood independently of estrogen changes (Swegle & Kelly, 2004). There are advantages to the use of this particular drug over estrogen and/or progestogen-containing treatment options, as it does not increase mammographic density, thus not increasing risk of breast cancer, whilst still having the effects on bone density and VMS seen in older HRT's (M. J. Reed & Kloosterboer, 2004). Part of the reason that Tibolone is thought to be such an effective treatment is its effects as an androgen replacement. Although estrogen therapy alone has shown positive effects on mood, testosterone imbalance may contribute to lack of well-being (Bromberger et al., 2010; Davis, 2002). The clinical reports are supportive of the efficacy of Tibolone in alleviating adverse mood symptoms experienced by postmenopausal women. To date, there is little research into the efficacy of Tibolone

during perimenopause. Given that a previously reported meta-analysis of estrogen therapy found a two-fold increase in the effect size in perimenopausal compared to postmenopausal women (Zweifel & O'Brien, 1997), there is good reason to believe that clinical results will be positive.

1.12 Limitations in the Existing Evidence Base and Conclusion

Despite ongoing debate, Perimenopausal Depression is a construct that has become widely accepted. The lack of certainty regarding the presence of a relationship between perimenopause and depression is partly due to the undeniably complex relationship between mood, estrogen and neurotransmitters. Methodological problems have also contributed to the lack of clarity regarding Perimenopausal Depression. The characterisation of depression has often been via self-report or has been confused with the somatic symptoms of perimenopause, with a lack of standardised and continuous measures of depression. Perhaps more problematic has been the lack of a clear definition of perimenopause and the stages within it. In 2001, the Stage of Reproductive Aging Workshop (STRAW) proposed a staging system for ovarian aging based on qualitative and menstrual criteria for define each stage (Soules et al., 2001a). This was revised and fine tuned in 2011 (S. D. Harlow et al., 2012). The impact of these methodological issues can be seen more clearly as we look at research from only 10 years ago when there were less stringent criteria for perimenopausal status. Where stressful life events were initially found to be the biggest predictor of depression during the midlife (Woods & Mitchell, 1997), more recent evidence has shown that perimenopausal status, severity of vasomotor symptoms, hormonal fluctuation and health and lifestyle factors are in fact more strongly related to depression during the midlife than stressful life events (L. S. Cohen et al., 2006; E. W. Freeman et al., 2006;

Fuh, Wang, Lee, Lu, & Juang, 2006; Woods et al., 2008).

The current lack of clarity regarding the nature of depression during the perimenopause, as well as the inconsistent evidence of causal factors related to Perimenopausal Depression, highlights this as a particular issue of need for further research. The similarities in symptomatology with depressive disorders occurring during other times of hormonal disturbance (e.g. PMS or postnatal depression) suggest a common underlying cause (potentially related to fluctuating gonadal hormone levels). This thesis therefore focuses in more detail on ascertaining what may cause depression during this time, as well as trying to establish whether it is quantitatively or qualitatively different from standard depression, and thus whether it requires a different treatment approach.

CHAPTER 2: LITERATURE REVIEW: FACTORS ASSOCIATED WITH DEPRESSION DURING THE PERIMENOPAUSAL TRANSITION

2.1 Preamble to Published Paper

This paper presents a portion of the literature review of this thesis. The aim of this paper was to provide an overview of the factors that have been associated with the development of symptoms of depression during perimenopause. Reviewed within this paper was literature that has identified various biological, psychological, lifestyle and social factors as predictors of depression during perimenopause. The implications of this research for both future studies and clinical practise are discussed.

This paper was published in the Archives of Women's Mental Health in August 2012. This journal is the official journal of the Marce Society and the North American Society for Psychosocial Obstetrics and Gynaecology (NASPOG). It is an interdisciplinary peer reviewed journal read by psychologists, psychiatrists, social workers, nurses, and other professionals who work within the field psychiatry and obstetrics-gynaecology. It is published by Springer.

Monash University

Declaration for Thesis Chapter 2

Declaration by candidate

In the case of Chapter 2, the nature and extent of my contribution to the work was the following:

Nature of contribution	**Extent of contribution (%)**
Literature review, project design and writing of paper	80

The following co-authors contributed to the work:

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Declaration by co-authors

The undersigned hereby certify that:

(1) The above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) They meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) They take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) There are no other authors of the publication according to these criteria;
(5) Potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
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REVIEW ARTICLE

What factors determine whether a woman becomes depressed during the perimenopause?

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Abstract Perimenopause has long been associated with psychological distress, both anecdotally and clinically. Research has identified this time as a period of increased risk for both first-episode depression and for depression reoccurrence. However, we know that the majority of women do not experience these difficulties during perimenopause. This review examines the current research literature looking at the factors associated with depression during perimenopause, with a view to identifying those factors which are protective and those factors which predict increased risk. From the literature, it is evident that some women have a hormonal vulnerability to mood disorders. However, this does not account for the phenomenon of perimenopausal depression in and of itself. Rather, there appears to be a complex interplay between hormonal vulnerability, the psychosocial resources one has (coping skills and social support), their overall well-being (exercise and other lifestyle factors) and the demands on their coping resources (stressful life events). The complexity of the relationship between perimenopause and depression means that there is a need to look beyond either as a sole explanation of mood during midlife. Education is required for both general practitioners and for women regarding the individual risks of psychological distress during perimenopause, as well as the knowledge of the life factors which we know to be protective.

Keywords Perimenopause · Depression · Risk factors · Protective factors · Psychosocial

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Introduction

Depression is the number one cause of disability worldwide, and women are twice as susceptible as men, with 10–23 % lifetime prevalence for women (Bromberger 2004; Noble 2005). Several risk factors for depression have been identified, including adverse life events, genetic predisposition and personality traits (Boyce et al. 1991; Kendler et al. 1995; Krendler et al. 2000). For women, the transition into menopause, known as perimenopause, has also been associated with an increased risk for both symptoms of depression (Bromberger et al. 2003; Cohen et al. 2006) and for major depressive episodes (Freeman et al. 2006a). Perimenopause occurs in most women during the ages of 40 to 55 years and is associated with a variety of biological and psychological changes. The most notable change associated with perimenopause is changes to, and eventual cessation of, the menstrual cycle. In addition, vasomotor, cognitive, metabolic and somatic changes take place, as well as changes in mood, irritability and hostility. These changes are brought about by hormonal changes. Fluctuating hormone levels are detected for around 2 years before any classic symptoms of perimenopause (menstrual irregularity and hot flashes) are reported. This fluctuating hormonal profile, rather than any overall decrease in the availability of hormones, is thought to be responsible for the symptoms of perimenopause. For the purposes of this review, perimenopause refers to the menopausal transition, beginning with variability to the menstrual cycle and continuing to the early postmenopausal years (up to 1 year amenorrhea) (Harlow et al. 2012).

The transition into menopause is anecdotally known as a time of psychological instability for women. Although the majority of women do not develop depression during perimenopause, it is a period of mood disturbance for a significant proportion (McKinlay et al. 1987). This is reflected in

the rates of depression during the perimenopausal years, with rates of first episode depression anywhere from 2 to 14 times higher than in the premenopausal years (Schmidt et al. 2000, 2004a; Cohen et al. 2006; Freeman et al. 2006b).

While for many women there is an increased risk of mild or major depression during perimenopause, the fact remains that the majority of women do not develop depression during perimenopause. This raises the question as to why some women seem to be more vulnerable than others. There are several theories that try to explain this epidemiological phenomenon, with previous explanations having focused on various biological, psychosocial and lifestyle factors. However, there is no clear-cut formula that can predict who will develop depression during this time. Rather, there are a number of factors that put women at risk of depression during the perimenopause, as well as factors which seem to be protective against it.

Psychological disturbance during the perimenopause

Studies from menopause clinics show that mood disturbance is the most common perimenopausal symptom, occurring in approximately 75 % of patients (Ayubi-Moak and Parry 2002). Research on the relationship between perimenopause and mood disturbance is mixed, with some longitudinal studies showing associations between psychological symptoms and perimenopause (Schmidt et al. 2004a; Freeman et al. 2006a) and others finding no such relationship (Woods and Mitchell 1997). This inconsistency can in part be attributed to methodological obstacles to do with determination of depression and perimenopausal status and endocrine heterogeneity (Parry 2008). Study differences in how perimenopause has been defined have also led to a lack of consistency between studies. For instance, some have used menstrual cycle characteristics, such as regularity and time since last menses, whereas others have used chronological age in which perimenopause occurs (Joffe 2003). Using age as a proxy for menopausal status is a crude measure as the age of onset of perimenopause varies from 35 to 55 years. Using menstrual cycle changes is a much more accurate definition of perimenopausal status, but even then it is not 100 % accurate. The only definitive way to know if a women has entered the perimenopause is by blood assays looking for increased follicle-stimulating hormone (FSH) serum level (FSH greater than 25 IU/L is indicative of gonadotropins' attempt to stimulate declining ovarian function; Soares et al. 2001). However, few studies have had the luxury of diagnosing perimenopause in this manner as the costs and invasive nature of the tests are prohibitive. In studies that have defined menopausal status by menstrual cycle characteristics (such as changes recent irregularity, or changes to flow and duration), it has been found that perimenopause doubles the risk for depressive symptoms compared to pre- and postmenopausal women (Avis et al. 1994). In addition, whilst cross-sectional studies have often not found a relationship between depression and perimenopause (McKinlay et al. 1987; Dennerstein et al. 1994; Woods and Mitchell 1997), prospective systematic studies have (Harlow et al. 1999). Standardized classification guidelines were proposed in 2001 (Soules et al. 2001), and then revised in 2010 (Harlow et al. 2012), known as the Stages of Reproductive Aging Workshop (STRAW), which have helped address the variability in perimenopausal status. STRAW defines the early transition into menopause as changes of seven or more days in menstrual cycle length, and late transition stage as two or more skipped menstrual cycles and 60 days or more of amenorrhea, and postmenopausal stage as 12 months or more of amenorrhea (Soules et al. 2001; Harlow et al. 2012). The particular stages of the transition have been associated with differing risk levels for depressive symptoms. Bromberger et al. (2007) found that the greatest risk period was the late transition, but they also found an increase in the early transition and the early postmenopausal years. Woods et al. (2008) also found that the late transition period was a period of significantly increased risk for depressive symptoms. Additionally, the presence of a relationship between depressive symptoms and perimenopause when following up women prospectively, but not when comparing women of different age groups cross sectionally, may indicate that cultural factors have a big impact on either reporting of symptoms or on the experience of symptoms. The experience of a woman who has lived through a particular cultural era may not be comparable to a woman from another generation, even though they may have in other ways had very similar demographics.

There is still compelling evidence for an increase in rates of depressive symptoms during the perimenopause, even when taking into account methodological issues and inconsistencies in the research literature. Freeman et al. (2004a) found that participants in the Penn Study of Ovarian Aging were more than four times more likely to have high Centre for Epidemiologic Studies Depression scale scores (>16) when in perimenopause compared with their scores before they entered perimenopause. Similarly, Cohen et al. (2006) found that women with no history of major depression who experienced hot flashes during the perimenopause were significantly more likely to become depressed than women who had not entered perimenopause. These results are supported by other epidemiologic studies that have found an increase in depressive symptoms in perimenopausal women compared with premenopausal women (Bromberger et al. 2001, 2003). Freeman et al. (2004a) found that women in perimenopause were up to three times more likely to report depressive symptoms than were premenopausal women. In a longitudinal study of asymptomatic premenopausal

women, Schmidt et al. (2004a) found that events related to late perimenopause, as opposed to early on in the transition, may be associated with an increased susceptibility to develop depression in some women. So, it seems that despite some inconsistencies within the field, the weight of the evidence is supportive of an association between depression and perimenopause.

Biological factors

Hormonal vulnerability

Most of the research into why some women seem to be vulnerable to perimenopausal depression revolves around fluctuating oestrogen levels. The co-occurrence of a spike in depression and changes to reproductive hormones intuitively suggest that an endocrine mechanism is involved in the aetiology of perimenopausal depression (Parry 2008). Schmidt et al. (2004a) found that during the 24 months surrounding the final menstrual cycle, women were 14 times more likely to develop depression than in the 30 years following puberty. Freeman et al. (2004a) found an increased risk for severe depression during the perimenopause compared with the premenopause or postmenopause, independent of variables such as past history of depression, vasomotor symptoms (VMS) and sleep quality. Whilst the declining levels of oestrogen were initially blamed for perimenopausal depression, oestrogen levels actually increase during the early perimenopausal period, before dropping again (Burger et al. 1999). This indicates that it is the *fluctuations* in reproductive hormones that trigger depression in vulnerable women. Through animal and human studies, and clinical data, it is known that the reproductive hormones progesterone and oestrogen and the neurotransmitter responsible for mood, serotonin, share common pathways and receptor sites in the brain (Schmidt et al. 1998; Bloch et al. 2000). This suggests that, for some women, there may be an underlining physiological susceptibility for mood difficulties related to reproductive events. In addition to the role of oestrogen and progesterone, research is increasingly highlighting the role of androgens on mood during the perimenopause. Santoro et al. (2005) found a relationship between circulating androgen levels and depressive symptoms, but not with depressive symptoms and estradiol, in the early stage of perimenopause. Higher testosterone levels have also been associated with higher levels of depressive symptoms, independently of menopausal status (Bromberger et al. 2010). Additionally, androgen-based therapies have been shown to improve mood in pre- and postmenopausal women (Almeida 1999; Goldstat et al. 2003), offering further potential for pharmacological intervention.

There seems to be a subset of women who have extreme sensitivity to changing hormone levels associated with the menstrual cycle, and these women are most vulnerable at times of intense endocrine change, specifically premenstrually, postnatally and perimenopausally. Community and clinic-based studies have shown that premenstrual syndrome (PMS), premenstrual dysphoric disorder and postnatal depression are risk factors for subsequent perimenopausal depression (Dennerstein et al. 1993; Stewart and Boydell 1993; Harlow et al. 1999). PMS has been identified as both an antecedent to as well as a frequent accompaniment of perimenopausal depression, leading to speculation that there is a tendency for some women to be at risk for mood destabilization during periods of reproductive endocrine change (Richards et al. 2006). Research has observed a higher-than-expected rate of PMS history in perimenopausal depressed women (Richards et al. 2006), and it has been identified as one of the strongest predictors of perimenopausal depression (Freeman et al. 2004a, b). However, in a prospective study, Schmidt et al. (2004a) were unable to identify an association between either PMS or postnatal depression with perimenopausal depression. An acknowledged problem in the literature is that many studies use retrospective self-reports of PMS, with many of these women, on closer inspection, not meeting criteria for PMS. This unreliability of self-reporting was highlighted by Richards et al. (2006) who found that upon investigation, the actual rate of premenstrual dysphoria was not predicted by initial self-reports. However, further support for a common underlying cause comes from the nature of menstrual cycle-related mood disorders. Common symptoms are shared by women complaining of PMS, postpartum blues, the perimenopausal transition and menopause: depression, sleep disturbance, irritability, anxiety and panic, memory and cognitive dysfunction and a decreased sense of well-being (Arpels 1996). Despite inconsistencies in the research, there is compelling evidence that a past history of mood disturbance related to reproductive-related events is a significant risk factor for perimenopausal depression. However, this past history of reproductive event-related mood disorders provides a far from complete picture of a woman's risk of perimenopausal depression.

Vasomotor symptoms

The symptoms most commonly associated with perimenopause are VMS, which refer to episodic flushing and sweating (Kronenberg 1990). About 75–85 % of women are affected by them during perimenopause. Most women experience them for up to a year, but up to 25 % of women experience them for 5 years or longer (Moline et al. 2003). Several factors have been found to influence the risk of experiencing VMS, a higher incidence is found in women with lower socio-economic status, poor health status, lower levels of education (Schwingl et al. 1994; Kuh et al. 1997)

and cigarette smokers (Holte and Mikkelsen 1991a; Kuh et al. 1997). This highlights the problems associated with VMS reporting. Namely, it is unclear what effect perceptions and expectations of VMS and menopause, as well as mood state, have on subsequent reporting.

Several studies have shown that the severity of VMS is a risk factor for perimenopausal depression. In a population-based prospective study, Cohen et al. (2006) found that the presence of VMS increased the risk for depressed mood during the perimenopause. However, while hot flushes are frequently associated with depression, they are not uniformly present. Over 80 % of perimenopausal women with depression experience comorbid VMS, compared to 49 % of perimenopausal women without depression (Joffe et al. 2002). This leaves 20 % of women experiencing perimenopausal depression who do not experience any VMS. In fact, hot flushes and perimenopause have been found to be *independent* risk factors for depression (Freeman et al. 2004a). In an observational study assessing the relationship between climacteric symptoms and psychosocial factors, Binfa et al. (2004) found that vasomotor and physical symptoms of the climacteric were related to perimenopause, whereas psychological symptoms were more influenced by psychosocial factors (mainly negative life events). This suggests that the relationship between VMS and psychological symptoms, if present, is limited. Öztürk et al. (2006) found no correlation between the severity of VMS and depression, suggesting that VMS do not predict either the severity or existence of depression, making this relationship uncertain. Bromberger et al. (2008) found that life stress and history of psychological symptoms were more important than VMS when predicting first lifetime episodes of major depression in midlife women, results which clearly undermine the significance of VMS. However, their findings also suggested that women who have a more symptomatic perimenopausal transition are at higher risk of a major depressive episode. In a longitudinal study by Hardy and Kuh (2002), it was found that VMS symptoms are strongly related to perimenopausal status, while psychological symptoms were more strongly related to current life stresses than perimenopause status. Further complicating the picture, it has also been suggested that VMS can be influenced by depression. A study by Igarashi et al. (2000) found that vulnerability to stress is associated with worse climacteric symptoms. Greene and Cooke (1980) reported that life stress in a normal population influenced the severity of perimenopausal symptoms *more significantly* than perimenopause. The often co-occurrence of severe VMS symptoms and depression during the perimenopause seems more likely to reflect a common underlying endocrine sensitivity, rather than a causal relationship between the two.

Sleep disruption has also been found to be a risk factor for perimenopausal depression. It has been theorised that depression during the perimenopause may be secondary to the sleep disruption caused by hot flashes and night sweats, referred to as 'the domino theory' of perimenopausal depression. Sleep disruption during perimenopause is ubiquitous, with reports ranging from 44–61 % of perimenopausal women reporting insomnia, compared to 33–36 % of premenopausal women (Brugge et al. 1989; Moline et al. 2003). Constant mild sleep deprivation could explain the decrease in mood and increase in irritability and hostility that are seen during perimenopause. Whilst hot flashes are the most commonly reported cause of sleep difficulties in perimenopausal women, their role is controversial and confusing. Studies have shown that perimenopausal women do experience more disturbed sleep and decreased sleep quality than premenopausal women, and this is likely attributable to VMS. Burleson et al. (2010) found that sleep problems predicted worse mood on the following day but accounted for only a small portion of the relationship between VMS and mood symptoms, suggesting that any effect of vasomotor symptoms on mood acts through a mechanism other than sleep disruption. It is worth noting that perceptions of sleep quality are affected by depression, making any conclusions from self-reports difficult to verify (Parry 2008). Perimenopausally depressed women have been shown to over-report severity of hot flashes during sleep, with skin conductance studies revealing that they have fewer and shorter hot flashes that disrupt sleep than do non-depressed perimenopausal controls (Parry et al. 2006). This suggests that anxiety about the experience of hot flashes, rather than their physiological experience, may be the more significant predictor of sleep disturbance in depressed perimenopausal women.

There is agreement in the literature that chronic sleep deprivation can lead to depression. However, insomnia is also one of the most common symptoms of depression, making this a bidirectional relationship. This is all true for the perimenopausal depressed woman. The relationship between the factors is complicated and highly interrelated. When taking into account the potential effect that VMS have on mood, as well as sleep, and of the depression associated with perimenopause independent of VMS and sleep, the picture becomes infinitely more complex. Despite evidence indicating a role of sleep disturbance and VMS in mood disturbance during the perimenopause, it still seems that this picture is incomplete. In a multiethnic community-based study, Bromberger et al. (2003) found that mood symptoms in perimenopausal women remained significant after adjusting for VMS and sleep disturbances.

Psychosocial factors

Past history of mood disorders

As discussed earlier, depressed mood during perimenopause is particularly related to previous episodes of depression associated with the menstrual cycle or periods of altered hormonal functioning, such as premenstrual syndrome and postpartum depression. However, it has also been shown that women who have experienced depression not in the context of reproductive events are more likely to experience perimenopausal depression. In fact, over half of women with perimenopausal depression have experienced a previous depressive episode (Cohen et al. 2006; Freeman et al. 2006a). In a longitudinal study, Avis et al. (1994) found that prior depression was the most predictive variable for subsequent depression in women aged 45–55 years. The evidence suggests that the Perimenopause increases susceptibility to depression, especially in women with a lifelong vulnerability.

Attitude toward menopause

Research has shown that the way in which women regard menopause and the expectations they have of the transition, affect their psychological wellbeing during the Perimenopausal period (Avis and McKinlay 1991; Hunter 1992; Woods and Mitchell 1996). In a prospective study, Avis and McKinlay (1991) found that women who have more negative attitudes to menopause go on to report more perimenopause symptoms and are more likely to become depressed. The experience of perimenopause is influenced by cultural factors, and our perception of it is highly dependent on social learning about what to anticipate during midlife (Woods and Mitchell 1996). In the Massachusetts Women's Health study (Avis and McKinlay 1991), premenopausal women who reported neutral feelings or relief about the prospect of menopause developed more positive attitudes after menopause. However, women with previously negative beliefs about perimenopause were more likely to develop severe climacteric symptoms. In a culture that values youth and holds negative views about ageing, it is not surprising that women may view this marker of midlife as a negative event. Research has demonstrated that a person's behaviour can be affected by their expectations, a concept known in psychological literature as 'self-fulfilling prophecy' (Avis and McKinlay 1991). Negative beliefs about menopause may act as a filter through which symptoms are experienced and thus influence women's perceptions of perimenopause (Hunter 1992). It is plausible that women's negative beliefs about the experience of perimenopause may contribute to an experience to match.

Stressful life events and the 'empty nest'

A relationship between stressful life events and the incidence of depression has been well documented in the literature (Hecht and Mensh 1975; Cohen 1987; Kendler et al. 2000). Some studies have suggested that the perimenopause and midlife are associated with significantly more stressful life events than are other stages of a woman's life (Schmidt et al. 2004b). In 1980, Greene and Cook found that perimenopausal women reported more negative life events than younger women. This observed increase in negative life events was predominantly related to events associated with interpersonal losses (e.g. children leaving the home and death of parents) and was consistent with the 'empty nest' construct. Several studies have found that the presence of negative life events is associated with perimenopausal mood and behaviour symptoms (Greene and Cooke 1980; Dennerstein et al. 2001). Based on this observation, it has been postulated that perimenopausal depression occurs secondary to an increase in negative life events (Greene and Cooke 1980; Cooke and Greene 1981).

The idea of the 'empty nest', when all the children leave the family home, has for a long time been thought of as a time of increased risk of depression in middle-aged women. However, rather than being perceived entirely negatively, it has been found that for many women, events associated with the empty nest construct are actually looked forward to (Barber 1989). Whilst historically when a woman's predominant role was to care for her family's needs, the period when children left home may have resulted in a negative reaction, there has been considerable social change over the last century (Dennerstein et al. 2002). In a longitudinal study, Dennerstein et al. (2002) found that, for the majority of women, the departure of the last child from the home was associated with positive changes to mood state and a reduction in daily hassles. Another important social change is that the average age of women when they have their first child is increasing steadily, with one in ten first-time mothers being over 35 years of age (AIHW 2003). Whilst in the past, perimenopause and departure of the first child used to coincide, we are now finding that women enter perimenopause when their children are still quite young (early to mid-adolescence). In addition, adult children are delaying leaving the family home until later and later, and are often returning after they have left. In Australia in 2006–2007, 31 % of people aged 20–34 years had left their parents' home and returned at some point to again live with their parents (ABS 2009). What this all amounts to is that the peak in depression in midlife no longer coincides with an 'empty nest', arguing against this lifestyle change being the most significant predictor of depression.

There is still an argument that during midlife, women experience more personal changes and/or life events than at

any other point in the lifespan (McKinlay et al. 1987). These experiences range from increased risk of illness or death of spouse, divorce or separation, unemployment, death of parents, to loss of social support (McKinlay et al. 1987). In a study by Woods and Mitchell (1997), it was found that a stressful life context was the most influential factor in accounting for depressed mood during midlife, with the perimenopausal transition offering little explanatory power. However, a study by Veeninga and Kraaimaat (1989) found that whilst women presenting to menopause clinics had higher reports of climacteric complaints and psychological symptoms than menopausal women not presenting to clinics, they did not report any more life events. However, the menopause clinic attendees did report more negative impact of life events than did non-attendees. This could suggest that some women are more susceptible to negative effects of stressful life events which then results in a more symptomatic perimenopause. However, it may signify an underlying hormonal vulnerability in some women which puts them at risk for depression, independently of other risk factors. It may be that the difference between perimenopausally depressed women and non-depressed women is in the way that they perceive life events, rather than simply the experience of the life event. Ballinger (1985) found that depressed perimenopasual women experienced a more negative impact of life events and more feelings of being stressed than a group of asymptomatic controls. Women who become depressed in perimenopause may therefore have a vulnerability, which as discussed previously may be an exaggerated sensitivity to endocrine fluctuations, that means they cope more poorly with the events making them more prone to mood disorders.

Coping styles

The way in which one copes with stress has been shown to moderate the relationship between perimenopause and mood. There has been considerable research examining how individuals cope with stress, particularly as this relates to risk of depressive episodes generally, and a very modest amount of research looking at the impact of coping styles on depression during the perimenopause. In regard to the research looking at depression more generally, there have been different coping styles identified as being more effective compared to others. Carver et al. (1989), in their multidimensional model of coping strategies, identified 13 main strategies that people use to cope in stressful situations. These included active coping, planning, suppression of competing activities, restraint coping, seeking of instrumental social support, seeking emotional social support, positive reinterpretation, acceptance, denial, turning to religion, focus on and venting of emotions, behavioural disengagement and mental disengagement. While Carver et al. (1989) did indicate that some strategies were more adaptive than others, they did not systematically categorize these strategies in terms of efficacy. Morse et al. (1998) found that based on self-reports of previous PMS history and subsequent reports of perimenopausal distress, the indication is that women who report high levels of symptomatic distress and disturbance during the menopause transition are those women who are less resilient, have higher levels of life stress and have less effective coping strategies. Neri et al. (1997) found that active and avoidant coping styles were associated with more severe VMS symptoms. In addition, Igarashi et al. (2000) found that an avoidance-oriented coping style was positively correlated to the severity of menopausal symptoms, and that an aggressive-expression coping style was associated with less severe symptoms. This suggests that ventilation of aggressive emotion may alleviate menopausal symptoms, which has implications for supporting perimenopausal women (Igarashi et al. 2000). Clearly, this has implications for therapeutic management of perimenopausal depression and irritability. However, more research clarifying the relationship between Perimenopausal depression and coping styles is clearly required. It seems likely that the psychological resources of an individual affect how they then cope during a period of increased vulnerability. It seems that those women who perhaps do not utilise the most helpful coping strategies are more likely to be negatively affected during periods of hormonal vulnerability.

Social support

Social support has been found to be an important modulator of perimenopausal depression. Good social support is thought to moderate the negative effect of life events during mid-life, which is consistent with what we know from looking more broadly at depression (Cooke 1985). Harlow et al. (1999) found that, relative to married women, women who have never been married or were divorced, widowed or separated were at a significantly higher risk of depression during perimenopause. In a study by Schmidt et al. (2004b), perimenopausal women who were depressed were compared with women who were not depressed. It was found that depressed perimenopausal women reported significantly less satisfaction with their significant others. However, it is unclear whether dissatisfaction in the primary partnership was pre-emptive of depression during the perimenopause, or whether the depression altered these women's perception of this relationship. In a longitudinal study, Dennerstein et al. (1999) found that risk factors for negative mood during midlife included interpersonal stress. Additionally, risk of negative mood was significantly lowered by positive feeling for their partner, gaining a partner and decreasing stress. Morse et al. (1998) found that medium to high levels of interpersonal stress were related to worse profiles of

perimenopausal symptoms. Ascertaining satisfaction with social support may therefore be an important indicator of potential for adverse mood.

Socioeconomic status, education and achievement

Socioeconomic status (SES), education and achievement are all known to be protective against depression (Murrell et al. 1983; Miech and Shanahan 2000). However, there is limited research that looks at the role of these factors for women during the perimenopausal years. In a cross-sectional study, Harlow et al. (1999) found that women who were currently employed and those living in higher SES areas were more likely to have lower depression scores. Research has also shown that higher educational achievement is associated with slightly decreased risk of depression in the perimenopausal years (Harlow et al. 1999; Choi et al. 2004). There are multiple possibilities that could explain the protective nature of higher education. It may be because women who are better educated are more likely to have a better understanding of both perimenopause and depression. Also, it could be that education offers an important resource to women, better enabling them to adapt to changes during perimenopause (Choi et al. 2004). Alternatively, it maybe that higher level of education is a proxy for a fulfilling career and that this is the factor which allows women to have a sense of purpose and meaning that goes beyond stereotypical gender roles (youthful, sexual woman or mother) that are compromised during the perimenopause (Raup and Myers 1989; Deeks and McCabe 2004). In fact, it is likely that all these possibilities hold some truth. This has important implications for interventions, indicating that they would be most effective if targeted to women of lower education status.

Lifestyle factors

Cigarette smoking

Cigarette smoking has been linked to an increased risk of depression across the lifespan. However, there seems to be evidence that smoking also specifically increases the risk of depressive symptomatology during the perimenopause. Harlow et al. (1999) found that women in the highest percentile of pack-years of cigarette smoking were significantly more likely than non-smokers to have higher depression scores during perimenopause. This increase in mood disturbance may be secondary to an increase in VMS associated with cigarette smoking, as cross-sectional studies have shown cigarette smoking is associated with increased VMS (Avis et al. 1997; Whiteman et al. 2003; Gold et al. 2004). Alternatively, one of the theories behind this increase in VMS with cigarette smoking is that cigarette smoking lowers endogenous oestrogen concentrations in the body (Whiteman et al. 2003), indicating that cigarette smoking may widen the window of hormonal vulnerability in certain women.

Exercise and body mass index

The relationship between exercise and depression is well established within the literature (see Daley (2008) for a review). However, a relationship between exercise and the experience of perimenopause is a relatively new concept. Research has found that there is an association between exercise and the experience of VMS. As part of a longitudinal study, Morse et al. (1998) found that exercise was *inversely* related to maximum numbers of perimenopausal symptoms. An observational study conducted by Thurston et al. (2006) found an association between exercise and VMS, with women who engaged in vigorous exercise and who had a history of depression experiencing less severe hot flushes. This relationship between vigorous exercise and hot flushes was not, however, found in women without a history of depression. In a cross-sectional study by Youngwhee and Hwasoon (2008), it was found that women who were more physically active reported significantly fewer VMS, a finding supported by others (Elavsky and McAuley 2005). However, Mirzaiinjmabadi et al. (2006) found no relationship between self-reported VMS and depression, with similar findings found by others (Wilbur et al. 1990; Sternfeld et al. 1999). Whilst the relationship between VMS and exercise is unclear, exercise does seem to decrease psychological and somatic symptoms of perimenopause. Dennerstein et al. (1994) found that women who exercised were less likely to experience menopausal symptoms, and others have demonstrated that physical activity can decrease psychological symptoms specifically (Brownson et al. 2000; Mirzaiinjmabadi et al. 2006; Youngwhee and Hwasoon 2008). Additionally, Harlow et al. (1999) found that increases in body mass index relate to modest increases in depression ratings, offering another potentially protective role for exercise. Whilst the mode in which exercise may impact on perimenopausal depression is unclear, its efficacy is of significance given the treatment potential.

Conclusions and implications

In addition to the conflicting theories, methodological problems have also contributed to the lack of a clear picture of perimenopausal depression. The characterization of depression has often been via self-report or has been confused with the somatic symptoms of perimenopause, with a lack of standardised and continuous measures of depression. Perhaps more problematic has been the lack of a clear definition of perimenopause and the stages within it. The impact of

these methodological issues can be seen more clearly as we look at research from only 10 years ago which had less stringent measurements to more recent research where some of the methodological obstacles have been addressed. Where stressful life events were initially found to be the biggest predictor of depression during the midlife (Woods and Mitchell 1997), more recent research has shown that perimenopausal status, severity of vasomotor symptoms, hormonal fluctuation and health and lifestyle factors are in fact more predictive of depression during the midlife than stressful life events (Cohen et al. 2006; Freeman et al. 2006a; Fuh et al. 2006; Woods et al. 2008). Research into pharmacological treatment of perimenopausal depression continues to make strides, with several best practice options for management now available (Parry 2010). But the anecdotally reported lack of understanding and education around perimenopause, and the subsequent distress around symptoms, is surprising given the ease with which it could be remedied. Women approaching their forties need to be having discussions with health practitioners about what to expect, what their risk might be and what can be done to prevent or reduce the severity of symptoms. Given that we can confidently identify many risk and protective factors, it makes sense that individuals at high risk could be identified and given preventative strategies around diet, exercise and social supports, which could help them through a potentially very difficult life period.

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CHAPTER 3: THE UNIQUE SYMPTOMATIC PROFILE OF PERIMENOPAUSAL DEPRESSION

3.1 Preamble to Submitted Empirical Paper

In Chapter 1 it was highlighted that there is ongoing debate as to whether Perimenopausal Depression is a unique form of depression that has a qualitatively (different symptoms) or quantitatively (different severity of symptoms) different symptom profile.

This chapter is the presentation of the first empirical study of the thesis, the aim of which was to provide a profile of the mood symptoms of Perimenopausal Depression, and to ascertain how these differ from symptoms experienced by women in the childbearing years. This was examined using a cross-sectional sample of women who were experiencing Perimenopausal Depression and comparing them to a sample of women experiencing depression during their childbearing years.

This paper significantly adds to the literature by providing a statistical assessment of subtle mood symptoms that differ between pre- and perimenopausal women, which has been missing to date.

This paper was submitted to Clinical Psychologist on the 6th of May 2013. *Clinical Psychologist* is the journal of the Australian Psychological Society's College of Clinical Psychologists. The journal covers a range of topics of broad general relevance to psychologists working in clinical and health settings, including assessment and treatment of psychopathology. *Clinical Psychologist* publishes state of the art reviews,

research papers, brief reports, and clinical case studies. The journal occasionally publishes special issues, guest edited by specialists, devoted to a single topic. It is published by Wiley.

Monash University

Declaration for Thesis Chapter 3

Declaration by candidate

In the case of Chapter 3, the nature and extent of my contribution to the work was the following:

Nature of contribution	**Extent of contribution (%)**
Literature review, project design and writing of paper	80

The following co-authors contributed to the work:

Name	**Nature of contribution**	**Extent of contribution (%) for student co-authors only**
Dr Stuart Lee	Review of paper drafts and general supervisory input	10
Professor Jayashri Kulkarni	Early conceptual ideas, review of paper drafts and general supervisory input	10

Candidate's Signature [redacted] **Date** **23/04/2013**

Declaration by co-authors

The undersigned hereby certify that:

(1) The above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) They meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) They take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) There are no other authors of the publication according to these criteria;
(5) Potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) The original data are stored at the following location(s) and will be held for at least five years from the date indicated below:
Locations(s) Monash Alfred psychiatry Research Centre

		Date
Signature 1	[redacted]	23/04/13
Signature 2	[redacted]	26/04/2013

3.3 The unique symptom profile of Perimenopausal Depression

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Abstract

Background

The period surrounding perimenopause is a time of increased risk for symptoms of depression in women. The experience of depression symptoms at this time is thought to be qualitatively different to that during the childbearing years, and to present with milder symptoms of depression, with increased agitation and fatigue. The research in this paper aimed to uncover whether Perimenopausal Depression can be distinguished from depression during the childbearing years based on the symptom profile.

Methods

Seventy-four depressed women who were either perimenopausal (n = 40) or in their childbearing years (n = 34) were recruited (M = 40.11; SD = 11 years). Participants completed a series of questionnaires relating to depression (Beck Depression Inventory-II), various mood states (Profile of Mood States) and changes in sleep patterns.

Results

Univariate relationships between symptoms and perimenopausal status were assessed. All significant variables at this level (anger-hostility, depression, tension-anxiety, fatigue-inertia and changes in sleep quality) were then analysed via logistic regression. The mood profile at these two different life stages could be differentiated from one another based on lower levels of depression symptoms and tension-anxiety, and increased levels of anger-hostility, fatigue-inertia and sleep disturbance in the perimenopausal women as compared to women in the

childbearing group.

Conclusions

This research provides support for the unique presentation of Perimenopausal Depression. The identification of a unique symptomatic profile provides different targets for intervention and potentially allows for different treatment options. Further research examining the role of hormonal changes in these differences is warranted.

Keywords: Perimenopause, Depression, Psychosocial

Introduction

Perimenopause refers to the reproductive stage immediately prior to menopause, and includes endocrine, biological and clinical changes, and ends in the year after the final menstrual period (Brambilla et al., 1994). The perimenopausal and early postmenopausal period has been shown to be associated with an increase in both depressive symptoms and episodes of major depression (Bromberger et al., 2011; Gibbs, Lee, & Kulkarni, 2012). In fact, during the perimenopausal period the rate of depression amongst women rises anywhere from 2 to 14 times higher than in the premenopausal years (L. S. Cohen et al., 2006; E. W. Freeman et al., 2006; Schmidt et al., 2000). There are several explanations for this increase in depression ranging from biological to psychosocial models. Research has also suggested a role for sleep disruption (Hollander et al., 2001), stressful life events (S. Cohen, 1987; Hecht & Mensh, 1975; Kendler, Thornton, & Gardner, 2000) and past histories of depression (Bromberger et al., 2011; L. S. Cohen et al., 2006; E. W. Freeman et al., 2006). The temporal association of lowered mood and perimenopause suggests that in some women, the changes in reproductive hormones associated with the perimenopause create a 'window of vulnerability', where women who are sensitive to changing gonadal hormone levels may be at a higher risk of becoming depressed (Lokuge et al., 2011; Soares, 2008). This comes from evidence showing that there is a subset of women who have heightened mood sensitivity to changing gonadal hormone levels associated with the menstrual cycle (Bloch et al., 2000; Lokuge et al., 2011; Rubinow et al., 1998). Such women are most vulnerable to depression at times of intense endocrine change, specifically the premenstrual, postnatal and perimenopausal periods (Richards et al., 2006). This theory is strengthened by research suggesting that women experience greater depression at these junctures, manifest by the symptoms of sleep disturbance, irritability, anxiety and panic, memory and cognitive dysfunction plus a decreased sense of wellbeing (Arpels, 1996). Based

on previous research, it is logical to expect that depression experienced during the perimenopause, as opposed to depression not associated with the reproductive cycle (i.e. during the childbearing years) may present as symptomatically different.

The perimenopausal period has distinct endocrine characteristics, with early perimenopause being a period of raised pituitary gonadotropin production: (Follicle Stimulating hormone (FSH), and Luteinizing hormone (LH) plus increased estradiol secretion. The later stages of perimenopause are characterised by high FSH levels and decreased estradiol production (Soules et al., 2001b). Reproductive status is often confirmed by the presence of elevated plasma gonadotropin, i.e., high FSH levels in the context of low plasma estradiol levels (Rubinow et al., 2007). In terms of the mood symptoms accompanying perimenopause, estrogen seems to have the most significant role through its modulation of serotonin, a neurotransmitter responsible for mood regulation (Rubinow et al., 1998). Estrogen has widespread actions throughout the central nervous system (CNS) and modulates the transcription of many enzymes, as well as the receptor proteins for many neurotransmitters and neuropeptides (Ciocca & Roig, 1995). As a result, estrogen regulates a great deal of serotonin activity. For example, estrogen modulates the synthesis of serotonin (I. R. Cohen & P. M. Wise, 1988), serotonin reuptake (Fink & Summer, 1996) serotonin receptor transcription (Sumner, 1995) and the response to serotonin stimulation (Matsuda et al., 1991). In addition to its effects on serotonin receptors, estrogen has been found to augment noradrenergic transmission (NA), a neurotransmitter responsible for regulating sleep and arousal (Deecher, Andree, Sloan, & Schechter, 2008). Estrogen increases NA turnover, decreases NA reuptake and decreases the number and sensitivity of dopamine (D2) receptors. The central serotonergic system, noradrenergic and the estrogenic system are prominently involved in the regulation of mood and behavioural states (Rubinow et al., 1998) and fluctuations in estrogen levels seen in

perimenopause may therefore directly cause many of the observed physical and psychological symptoms through altered activation of the key areas of the CNS.

If the significant increase in depression symptoms during perimenopause is predominantly seen as a result of gonadal hormonal fluctuations and thus aetiologically distinct from depression during the childbearing years, it seems feasible to consider that the presentation and symptoms would vary accordingly. Clinically, women with depression related to the perimenopause experience different symptoms compared to women experiencing depression symptoms at other stages of life (Schmidt, Roca et al. 1997). Despite speculation for over a century, the qualitative differences between depression during pre and peri-menopause have not received much attention within the literature. Clinically, the depressive symptoms experienced during the perimenopause have been described in terms of dysphoric mood, characterized by feeling blue or depressed, irritable or grouchy, tense or nervous (Bromberger et al., 2003; Brown, Sweeney, Loutsch, Kocsis, & Frances, 1984; Schmidt, Roca, Bloch, & Rubinow, 1997). Worsley, Davis et al (2012) described the clinical presentation of Perimenopausal Depression as an 'on-off' phenomenon with episodes of sadness or irritability lasting for minutes to hours before spontaneously resolving. Studies have also found that compared to pre-menopausal depression, Perimenopausal Depression has different levels of irritability and hostility (Bromberger et al., 2003; E. W. Freeman et al., 2008; Kornstein et al., 2010), increased mood lability (Holte & Mikkelsen, 1991), increased anxiety (Bromberger et al., 2013), and anhedonia (Ozturk et al., 2006) and is characterized by a milder presentation compared to that of a major depressive episode (Dennerstein et al., 1993b).

The nature of mood difficulties experienced by women in the perimenopause potentially has major implications for the diagnosis, pharmacological treatments, and psychological interventions. Despite this significance, there is a paucity of research regarding symptomatic differences in Perimenopausal Depression. By contrasting the qualitative differences in the symptom presentation of Perimenopausal Depression and depression symptoms experienced during the childbearing years; better-tailored treatments can be derived. This study aims to clarify if there are qualitative differences in mood disturbances between women in their childbearing years and women currently transitioning through perimenopause. Based on previous literature in this area, it was hypothesised that the childbearing age and perimenopausal groups would differ significantly on several variables including: severity of depression; level of anxiety; level of hostility; change in sleeping patterns; and level of fatigue.

Method

Participants

This study was conducted as part of a wider project using a cross-sectional sample design. Women were included who currently identified themselves as experiencing depression, and who were or were not currently perimenopausal (n = 34), and who identified themselves as experiencing depression and who were in the perimenopausal transition (n = 40).

All women who were included were currently physically well, able to give informed consent, were over the age of 18, were proficient in English, and were experiencing symptoms of depression. Women were considered to be in the perimenopausal/early postmenopausal transition if they were experiencing irregular menstrual bleeding; if their last menstrual cycle was within the last 2 years and/or they continued to experience vasomotor symptoms (hot flushes etc: S. D. Harlow et al., 2012; Holman et al., 2002; Mansfield, Carey, Anderson, Barsom, & Koch, 2004). The criteria to be included in the depression group was a Beck Depression Inventory II (BDI-II) score above 13. Women who were experiencing postnatal depression were excluded from the study. The data from these participants was screened before analysis to ensure missing data were random in occurrence and that all data was within expected ranges.

Procedure

Ethical approval for this project was obtained from The Human Ethics Committee of the Alfred hospital, Melbourne, as well as from The Ethics Committee of Monash University, Melbourne. Women were recruited predominantly through the Monash University community, via advertisements in electronic newsletters and posters. Several advertisements and posters were

also displayed at menopause clinics, on depression websites, and at community health centres. Individuals interested in participating were asked to contact the researchers via email or telephone details provided, at which point they were provided with details regarding the goals and rationale of the study and the requirements for participating. If participants indicated that they were still interested in participating, a questionnaire pack was sent out to the mailing address they provided. Included in this pack included a participant information and consent form, a series of questionnaires, and a reply paid envelope addressed to the researchers. Upon researchers receiving completed questionnaire, participants were sent a $20 gift card. Data was collected from August 2010 to February 2012**.**

Measures

Psychopathology was assessed using a series of questions regarding current and past history of mental health difficulties, as well as a series of questionnaires looking at current mood states. The BDI-II (Beck, Steer, & Brown, 1996) is a 21-question multiple-choice self-report inventory, which asks how the subject has been feeling in the last week. Each question has a set of at least four possible answer choices (0-3), ranging in intensity. For example: (0) I do not feel sad, (1) I feel sad, (2) I am sad all the time and I can't snap out of it, or (3) I am so sad or unhappy that I can't stand it. The total score is then used to estimate the level of depression, i.e. minimal depression (0-13), mild depression (14-19), moderate depression (20-28), and severe depression (29-63). This scale is one of the most widely used instruments for measuring the severity of depression. Reliability and validity of the BDI-II has been confirmed in several studies (Osman et al., 1997; Storch, Roberti, & Roth, 2004). Additionally, item 16 of the BDI-II that assesses changes to sleep pattern was used as an indicator of sleep quality or sleep disruption. Participants rated any changes (including increased and decreased sleep) in sleeping patterns using the four-point Likert scale, with ‘0’ indicating no changes to sleep, and ‘3’

indicating major changes.

The Profile of Mood States (POMS: McNair, Lorr, & Droppleman, 1971) is a widely used self-report measure of transient mood states. Consisting of 65 words or brief phrases, it asks participants to indicate on a 5-point Likert scale ranging from 1 (Not at all) to 5 (Extremely) how much they identify with each word or phrase on the current day. It consists of six scales including tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia and confusion-bewilderment. Several studies have shown reliability and validity of the POMS to be good (Baker, Denniston, Zabora, Polland, & Dudley, 2002).

Results

Sample Characteristics

The participants had a mean age of 40.11 years (SD = 11 years) with a range between 18 and 58 years. The Perimenopausal Depressed group had a mean age of 48.6 (SD = 4.9) and the childbearing depressed group had a mean age of 30.18 (SD = 7). The majority of participants were married with children, and had completed a postgraduate level of education and were working full or part time (see Table 1). The mean BDI-II score for the Perimenopausal Depressed group was 21.8 (SD=0.95), and for the Childbearing Depressed group it was 26 (SD=1.7).

Table 1. Descriptive demographic statistics of sample (N= 74)

	N (%)
Marital status	
Single	10 (13.5)
Married	30 (40.5)
De Facto	7 (9.5)
Boyfriend/girlfriend	12 (16.2)
Separated/divorced	14 (18.9)
Widowed	1 (1.4)
Children	
Yes	45 (60.8)
No	29 (39.2)
Employment	
Not employed	6 (8.1)
Casual/contract	11 (14.9)
Part time	20 (27)
Full time	37 (50)
Income	
<20,000	6 (8.1)
21-40,000	6 (8.1)
41-60,000	16 (21.6)
61-80,000	14 (18.9)
81-100,000	13 (17.6)
>100,000	19 (25.7)
Education	
Did not complete high school	2 (2.7)
Completed high school	8 (10.8)
Began university/TAFE	4 (5.4)
Completed TAFE degree/diploma	5 (6.8)
Completed university degree	15 (20.3)
Began postgraduate degree	11 (14.9)
Completed postgraduate degree	29 (39.2)

Inter-correlations among mood symptoms

In the first stage of analysis, relationships between the 6 POMS scales, BDI-II and changes to sleep patterns were assessed using Pearson correlations to check for co-linearity (See Table 2). Very strong inter-correlations were found between the POMS Depression scale and BDI-II, raising the possibility of co-linearity if entered together into a multivariate regression model. As the BDI-II is a more well-validated measure of depression, the POMS depression scale was excluded from the analysis.

Table 2. Inter-correlations between symptom variables (N=74)

	BDI-II	Sleep	Tension	Depression	Anger	Fatigue	Confusion	Vigour
Sleep pattern	.27*							
Tension-Anxiety	.59*	.16						
Depression-Dejection	.82**	.09	.65**					
Anger-Hostility	.61**	.21	.38**	.71**				
Fatigue-inertia	.48**	.21	.5**	.44**	.52**			
Confusion-bewilderment	.66**	.17	.73**	.78**	.62**	.51**		
Vigour-activity	-.11	-.03	-.01	-.89	.16	.9	-.07	

* $p < .05$
* $p < .001$

Univariate and Multivariate predictors of Group Status

Use of HRT and Oral Contraception was screened to see if they impacted BDI-II scores and no significant effects were found. Logistic regression was performed to assess the impact of 7 predictor variables (depression, sleep quality, tension, anger, fatigue, confusion and vigour) on the likelihood that respondents were perimenopausal or in their childbearing years. The full model containing all predictors was statistically significant, χ^2 (7, N = 74) = 30.32, p <.001, indicating that the model was able to distinguish between group status. The model as a whole

explained between 34% (Cox and Snell R square) and 45% (Nagelkerke R squared) of the variance in group membership, and correctly classified 75.7% of the cases. As shown in Table 3, five of the independent variables made a unique contribution to the model (tension, anger, depression, fatigue and sleep quality).

Table 3. Logistic Regression Predicting Likelihood of Group Membership (Perimenopausal or childbearing; N=74)

	B	S.E.	Wald	*p*	Odds Ratio	95.0% C.I. for Odds Ratio	
						Lower	Upper
BDI-II	-0.12	.06	3.88*	.049	0.89	0.79	1.00
POMS Tension	-0.16	.06	5.73*	.017	0.86	0.76	0.97
POMS Anger	0.12	.05	5.70*	.017	1.13	1.00	1.24
POMS Fatigue	0.13	.06	4.39*	.036	1.14	1.01	1.30
POMS Confusion	-0.11	.10	1.25	.264	0.89	0.74	1.09
POMS Vigor	0.06	.06	0.95	.329	1.06	0.94	1.20
Sleep quality	0.70	.36	3.40*	.048	2.01	1.01	4.04

* $p < .05$

Discussion

This research aimed to uncover whether the symptom profile of women who are perimenopausally depressed can be distinguished from that experienced by women during the childbearing years. It was found that depression symptoms at these two different life stages could be differentiated from one another based on levels of depression, tension-anxiety, anger, fatigue-hostility, fatigue-inertia and sleep disturbance.

The perimenopausal group was found to be have lower levels of depression symptoms than the pre-menopausal women, which is consistent with the anecdotal reports of a milder mood presentation in Perimenopausal Depression, characterized by feeling "blue" or depressed (Bromberger et al., 2003; Dennerstein et al., 1993a). There were higher levels of tension-anxiety found in the childbearing group. Previous research has shown that anxiety levels are higher through the perimenopausal years in comparison to pre-menopausal women (Tangen & Mykletun, 2008), although this research did not looked at women who were experiencing depression during perimenopause. Similarly looking at a non-depressed sample, Bromberger et al. (2013) found that in women with high anxiety levels premenopause there was no increase associated with entering perimenopause, but in women with low premenopausal anxiety levels there was an increase in anxiety perimenopause. These differences in the literature may stem from the different clinical samples used, i.e. depressed versus non-depressed samples. The relationship between anxiety symptoms and perimenopause is admittedly poorly understood (Bauld & Brown, 2009), and these results warrant further investigation. Anger-hostility was found to be higher in the perimenopausal group, which is consistent with previous research that has looked more specifically at irritability (Bromberger et al., 2003; E. W. Freeman et al.,

2008), but are inconsistent with the work of Kornstein et al. (2010), who found that irritability was increased in the premenopausal years, as compared to perimenopausal. This is possibly due to sample differences, with Kornstein et al. (2010), investigating a sample of women with a diagnosis of a Major Depressive Disorder. Additionally, they used age to determine menopausal status, which has been shown to be a poor indicator of perimenopausal status (Kornstein et al., 2010). The higher levels of irritability and hostility found in the present study are likely explained by the relationship between aggression and the CNS serotonin system function. Spyropoulou et al (2009) found a significant correlation between FSH and LH levels and outward irritability, which may be related to the self-reported experience of anger-hostility. The higher levels of disturbed sleep in the perimenopausal group is also consistent with past research, with reports of sleep disruption during perimenopause ranging from 44% to 61%, compared to 33-36% of premenopausal women (Brugge et al., 1989; Moline et al., 2003). What is interesting about the results of this research is that it was found that the levels of fatigue in the perimenopausal group were higher than the childbearing group independently of sleep disturbance. This is consistent with clinical observations that women experiencing depression symptoms during the perimenopause report above and beyond what would be expected due to reduced sleep quality (Schmidt, Roca et al. 1997). Fatigue has been found to be a common symptom of hormonally driven mood disturbances, including premenstrual syndrome and postnatal depression, and adds evidence for the role of hormonal disturbance as a causative factor for Perimenopausal Depression (See Payne, 2003 for a review).

What we see from these results is that Perimenopausal Depression is characterized by milder levels of depression and anxiety levels, increased hostility, sleep disturbance, and levels of fatigue above what would be expected due to sleep disturbance. Given that this research has found that symptoms of depression during perimenopause are symptomatically different in

presentation to depression in the childbearing years, it seems logical that a different aetiology of depression at this time is present as well. Certainly the symptom profile found in this research can be linked to underlying neurochemical pathways associated with the hormonal changes of perimenopause. These potential differences in mechanisms underpinning Perimenopausal Depression are particularly relevant when we look at treatment, as it is reasonable to assume that they may benefit from a different approach to treatment. This is particularly relevant to clinicians seeing women who are depressed during perimenopause, as the inclusion of a General Practitioner or specialist in the care plan may be warranted. Hormone replacement therapies have been shown to be particularly helpful for this cohort and may be a beneficial addition to treatment (Worsely et al., 2012). Further, an approach that incorporates distress tolerance, such as Mindfulness, may offer women more strategies to cope with the discomfort of perimenopausal symptoms.

Whilst the results of this study are promising, the study design limits the conclusions that can be drawn. As perimenopausal status was based on self-reporting, we cannot be completely confident that women would have met hormonal criteria for perimenopause or early postmenopausal (See STRAW criteria: S. D. Harlow et al., 2012). Ideally, future research would conduct thorough clinical interviews and/or hormonal assays to clarify a woman's biological perimenopausal status. Hormone assays may also be able to further clarify the relationship between female hormones and each symptom, i.e., whether women who had particularly low levels of estrogen are more vulnerable to symptoms of depression or fatigue. Sample size was also a limitation and this limited the power and sophistication of statistical analyses.

This research assists in demonstrating that symptoms of depression during the perimenopause may present in a somewhat different way to those experienced during the childbearing years.

This difference is probably related to the marked hormonal and biological changes that are characteristic of perimenopause. The identification of a unique mood symptom profile provides different targets for intervention plus different treatment options. In the future, an increased understanding of the biological processes underpinning Perimenopausal Depression will allow for better targeted hormone treatments, as well as the use of non-pharmacological interventions, such as exercise and diet. Insights about the symptoms of perimenopause have the potential to provide choices for women who struggle with symptoms of depression in mid-life, and who may struggle with the current antidepressant treatment regimens available to them. The potential for improvement in mood, with better understanding and treatment of Perimenopausal Depression as well as the quality of life and productivity, is substantial.

Key points

- Symptoms of depression during perimenopause were found to present as subtly different to that seen during the childbearing years, with milder symptoms of depression, increased anger, reduced sleep quality and increased fatigue that was independent of sleep quality.
- Owing to perimenopause being a period of marked hormonal fluctuations that for many women result in increased vasomotor, mood or somatic symptoms, consideration of biological contributions to presenting depressive symptoms is important and should be targetted therapeutically.
- Psychologists treating perimenopausal patients should be mindful of the potential for biopsychosocial causes of depressive symptoms when providing care and include General Practitioner's or specialists in the treatment plan where appropriate.

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Conflict of Interests

Jayashri Kulkarni, Stuart Lee and Zoe Gibbs declare that they have no conflict of interest.

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CHAPTER 4: PREDICTIVE AND RISK FACTORS FOR DEVELOPING DEPRESSION DURING THE PERIMENOPAUSAL TRANSITION

4.1 Preamble to Submitted Empirical Paper

This chapter is the presentation of the second empirical study of the thesis. The aim of this study was to ascertain the biological, psychological, social and lifestyle factors that are associated with symptoms of depression during perimenopause in a sample of Australian women. The intention of this study was to address the need, as outlined in Chapter 2, for a comprehensive understanding of the risk of Perimenopausal Depression. This was examined using a cross-sectional sample of perimenopausal women who were experiencing depressive symptoms and comparing them to a sample of perimenopausal women who reported no symptoms of depression.

This paper significantly adds to the literature by analysing a large number of factors and determining the unique contribution of each to the development of Perimenopausal Depression.

This paper was re-submitted on request to the Women's Health Issues on the 11th of March 2013. Women's Health Issues (WHI) is a peer-reviewed, bimonthly, multidisciplinary journal that publishes research and review manuscripts related to women's health care and policy. It is the official journal of The Jacobs Institute of Women's Health, and is dedicated to improving the health and health care of all women throughout the lifespan and in diverse communities. The journal seeks to inform health services researchers, health care and public health professionals, social scientists, policymakers, and others concerned with women's health. It is published by Elsevier.

Monash University

Declaration for Thesis Chapter 4

Declaration by candidate

In the case of Chapter 4, the nature and extent of my contribution to the work was the following:

Nature of contribution	**Extent of contribution (%)**
Literature review, project design and writing of paper	80

The following co-authors contributed to the work:

Name	**Nature of contribution**	**Extent of contribution (%) for student co-authors only**
Dr Stuart Lee	Review of paper drafts and general supervisory input	10
Professor Jayashri Kulkarni	Early conceptual ideas, review of paper drafts and general supervisory input	10

Candidate's Signature [redacted] **Date** **23/04/2013**

Declaration by co-authors

The undersigned hereby certify that:

(1) The above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) They meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) They take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) There are no other authors of the publication according to these criteria;
(5) Potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) The original data are stored at the following location(s) and will be held for at least five years from the date indicated below:
Locations(s) Monash Alfred psychiatry Research Centre

		Date
Signature 1	[redacted]	23/04/13
Signature 2	[redacted]	26/04/2013

4.3 Risk factors associated with depression during the perimenopausal transition

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Abstract

Background

This paper examines the factors associated with depression during the perimenopausal transition, to increase the understanding about the aetiology of perimenopausal depression.

Method

Seventy-six peri- and early post-menopausal women who were either depressed or not depressed were recruited (*Mean years* =49.5; *SD* = 4.3). Participants completed a series of questionnaires relating to depression (Beck Depression Inventory-II), perimenopausal symptoms (Greene Climacteric Scale), social support, life events, history of mood disorders, exercise regime, and questions regarding lifestyle and wellbeing.

Findings

Univariate relationships between predictors and depression scores were assessed. All significant variables at this level (history of depression, history of PMS, recent negative life events, aerobic exercise, social support and somatic symptoms) were then analysed via multiple regression. The presence of recent negative life events, a history of depression and severity of somatic symptoms of perimenopause were all found to predict unique variance in depression scores. There was also a trend towards a protective role of aerobic exercise.

Conclusions

This study confirmed the role of negative life events, previous depression history and

somatic complaints in the development of depression during perimenopause. Further exploration of this relationship is warranted.

Keywords: Perimenopause, Depression, Risk Factors, Protective Factors, Psychosocial

Introduction

The transition into menopause, known as perimenopause, has been found to be a time of vulnerability for women to develop depression. Occurring in most women between the ages of 40 to 55 years, the perimenopausal period is accompanied by significant changes in hormonal milieu, including fluctuating Follicular Stimulating Hormone (FSH) and estrogen levels, resulting in changes to, and ultimately cessation of, the menstrual cycle. Associated with these hormonal fluctuations are a variety of biological and psychological changes, including vasomotor (hot flashes, night sweats), cognitive (increased confusion and forgetfulness), metabolic (lowered metabolism, decreased energy levels) and somatic changes (aches and pains, headaches), as well as changes in mood, irritability and hostility. Beyond the known mood disturbance associated with perimenopause, there is also an increased risk of both reoccurrence and first episode of depression. The rates of women experiencing their first episode of depression during the perimenopausal years have been found to be anywhere from 2 to 14 times higher than in the premenopausal years (Bromberger et al., 2011; L. S. Cohen et al., 2006; E. W. Freeman et al., 2006; Schmidt, Haq, et al., 2004; Schmidt et al., 2000). Nonetheless, whilst many women become depressed during perimenopause, most women do not. The reasons as to why some women are more vulnerable to depression during perimenopause remain controversial.

The causative models for depression can broadly be categorised into one or more of the following: biological, cognitive-behavioural, and stress-vulnerability (known as the diathesis-stress model). In biological models, depression is seen as a consequence of genetic vulnerability or from disturbances of the biochemical, neuroendocrine, immune,

or chronobiological systems (Schotte, Van Den Bossche, De Doncker, Claes, & Cosyns, 2006). Cognitive-behavioural models attribute depression to negative and often dysfunctional thinking processes and subsequent maladaptive behaviours (Beck, 1979). In the diathesis-stress model, depression is thought to be the result of stresses that overwhelm the coping resources of the individual. This theory incorporates the impact of stressful life events on depression.

The most well researched and strongly supported theory of depression during perimenopause is the biological model (See Lokuge et al., 2011 for a review). Most biological theories are underpinned by the role of reproductive hormones on various central nervous system processes. There is a well-documented relationship between estrogen and serotonin, one of the primary neurotransmitters associated with mood regulation (Lokuge et al., 2011; Rubinow et al., 2007; Rubinow et al., 1998). Estrogen modulates the synthesis of serotonin (L. S. Cohen & P. M. Wise, 1988), serotonin reuptake (Fink & Summer, 1996), serotonin receptor transcription (Sumner, 1995) and the response to serotonin stimulation (Matsuda et al., 1991). Additionally, estrogen is known to have many interactions with noradrenaline, a neurotransmitter that modulates energy levels, regulates sleep and arousal (Deecher et al., 2008), offering a potential mechanism for fluctuations in estrogen impacting on the vegetative symptoms often experienced in depression. Further evidence for the role of hormones comes from studies finding a relationship between the incidences of premenstrual syndrome (PMS), premenstrual dysphoric disorder (PMDD), postnatal depression, and perimenopausal depression, suggesting a common underlying etiology (Dennerstein et al., 1993b; Bernard L Harlow et al., 1999; Stewart & Boydell, 1993). This relationship is, however, not conclusive, as a prospective study, Schmidt et al. (2004) was unable to identify an

association between either PMS or postnatal depression with perimenopausal depression.

Turning to the cognitive-behavioural model of depression, evidence suggests that during perimenopause there is an increased risk of relapse into depression for women with a lifelong vulnerability. In several studies, it has been found that over half of women with perimenopausal depression have experienced a previous depressive episode (L. S. Cohen et al., 2006; E. W. Freeman et al., 2006) and that prior depression was the best predictor of subsequent depression in women aged 45-55 years (Avis et al., 1994). This suggests a possible vulnerability in cognitive style or coping mechanisms that predisposes women to recurrent episodes of depression. Research has found that premenopausal women who have a negative attitude towards menopause have an increased risk of depression during the transition, indicating that a woman's expectation of perimenopause is directly related to her experience (Avis & McKinlay, 1991). Additionally, women with an external locus of control (i.e., those who lack a sense of control over their lives and their experience of perimenopause) are more likely to experience depression during perimenopause (Derry, 2004; Reynolds, 1999). Thus coping style or cognitions experienced in relation to perimenopause may also impact on risk for developing depression during perimenopause.

The stress-diathesis model has been shown to be transferrable to perimenopausal depression, with environment and social support having been found to moderate the risk of depression during perimenopause (Cooke, 1985). It has been suggested that women experience substantially more negative life events during midlife compared to other life stages (children leaving home, marital breakdown, death of parents), and this may be

responsible for increases in depression during this time (Greene & Cooke, 1980). Although evidence for a causal relationship is limited, negative life events have been associated with depression during perimenopause (Schmidt, Murphy, et al., 2004). Social support has also been shown in the depression literature to be an important protective factor (Aneshensel & Stone, 1982). It has been postulated that a good social support system can moderate the negative impact of life events and thus decrease psychological distress during perimenopause as a result (Cooke, 1985). Previous studies focusing on perimenopause, however, have not found that levels of social support influence depression (Binfa et al., 2004). Looking more broadly at midlife women, Cyranowski et al. (2012) found that comorbid Major Depressive Disorders and anxiety was associated with lower levels of social support, higher levels of distress, as well as lifetime histories of psychiatric disorders. The consistency of the relationship between social support and depression risk is therefore currently unclear.

The idea that depression arises as a stress reaction to the experience of severe somatic and vasomotor symptoms has also been proposed. Somatic symptoms accompanying perimenopause include muscle aches and pains, headaches, light-headedness or faintness, and difficulties breathing. Vasomotor symptoms (VMS), refer to episodic flushing and sweating, which affects 75-85% of women during perimenopause (Kronenberg, 1990), although findings of a relationship between VMS presence or severity and depressive symptoms are varied. Several studies have found that the severity of VMS are related to increased rates of depression during perimenopause (L. S. Cohen et al., 2006; Joffe et al., 2002). Other studies have suggested that the relationship between VMS and depression is limited at best, and that a more somatically symptomatic perimenopausal transition was more predictive of a major depressive

episode than were VMS symptoms (2009). In a prospective longitudinal study, Strauss (2011) found a reciprocal relationship between the symptoms of perimenopause and depression. Women who experienced more symptoms of depression premenopausally were at heightened risk of experiencing a more symptomatic perimenopausal transition, and those women who experienced a more symptomatic perimenopausal transition were then at higher risk of depressive symptoms at this time (Strauss, 2011). Further studies to help understand and clarify the nature of the relationship between perimenopausal symptoms and depression are warranted.

A relationship between perimenopausal depression and exercise has also been previously described, and this effect may be explainable by all three models of depression. Brownson, Eyler et al. (2000) found that there was a significant inverse relationship between exercise and somatic and psychological symptoms during perimenopause. It is possible that exercise has a neurobiological impact with changing levels of endorphins, monoamines and stress hormones in the brain, which results in increased positive mood or protection against stress hormone induced brain changes (Cotman & Berchtold, 2002; Duclos, Gouarne, & Bonnemaison, 2003). Exercise may also be having an effect via less direct means, by reducing overall stress and improving mood symptoms as a flow on effect (Salmon, 2001). Alternatively, increases in exercise may reduce depression through the necessary behavioural activation involved. The cognitive-behavioural model of depression asserts that when individuals increase the number of both pleasant activities and positive interactions with their social environment, the effect will include a decrease in the reported depression (Lewinsohn, Biglan, & Zeiss, 1976). Exercise is often enjoyable and has a social element that may independently impact positively on the risk of developing depression (Mead et al.,

2010).

The currently available evidence about the determinants of depression during perimenopause highlights a number of inconsistencies. This paper aims to concurrently investigate the extent to which multiple factors are independently associated with increased risk of depression during the perimenopausal transition, to assist in addressing this inconsistency. It is hoped that this research will help clarify the role and magnitude of various predictors, and help to develop a more comprehensive model of perimenopausal depression.

Method

Participants

This study was conducted as part of a wider project using a cross-sectional sample design to look at women who currently identify themselves as perimenopausal and/or as suffering from symptoms of depression (n = 145). Women were recruited predominantly through the Monash University community and Alfred hospital, both in Melbourne. There were, however, several interstate participants. All women who were included were currently physically well, able to give informed consent, over the age of 18, were proficient in English, and were perimenopausal or early postmenopausal (*n = 76).* Women were included if they were experiencing irregular menstrual bleeding; if their last menstrual cycle was within the last 2 years and they continued to experience VMS (Holman et al., 2002; Mansfield et al., 2004). Forty-seven percent of the overall sample was identified as currently experiencing symptoms of depression, based on Beck Depression Inventory II (BDI-II) scores above 13 (Beck et al., 1996)

Measures

Demographic variables included age, relationship status, education, occupation, and current occupational status. Additionally, the questionnaire asked about their exercise regime, any history of past mood disorders or menstrual cycle related mood disorders.

Psychopathology was assessed using a series of questions regarding current and past history of mental health difficulties, as well as a series of questionnaires looking at current mood states. The BDI-II (Beck et al., 1996) served as the primary measure of current depression severity and is a 21-question multiple-choice self-report inventory,

which asks how the subject has been feeling in the last week. This scale is one of the most widely used instruments for measuring the severity of depression. Reliability and validity of the BDI-II has been confirmed in several studies (Osman et al., 1997; Storch et al., 2004).

Recent Life Events were recorded using the Life Experience Survey (LES; Sarason, Johnson, & Siegel, 1978), which is a questionnaire assessing the presence of 57 events (both positive and negative) that are known to be stressful (i.e. 'death of a close family member' and 'outstanding personal achievement'). If present in the last 6 months, participants are then asked to rate the extent to which they viewed the events as having either a positive or negative impact on their life using a 7-point Likert scale from -3 (Extremely Negative) to +3 (Extremely Positive).

Symptoms of perimenopause were assessed using the S (Somatic) and V (Vasomotor) scales of the Greene Climacteric Scale(GCS; Greene, 1998), which is a brief checklist (21 items) providing an objective measure of mood disturbance, hot flushes, night sweats and vaginal dryness. Only the scales looking at the physical symptoms of perimenopause were utilised, as symptoms of psychological distress were captured using the BDI-II. On the GCS, symptoms are listed and then each symptom is rated by the respondent according to its severity using a four-point scale: not at all (0); a little (1); quite a bit (2); and extremely (3). Six scores are obtained relating to six categories of symptoms: 'Psychological distress' (broken down into 'anxiety' and 'depression'), 'somatic symptoms', 'sexual dysfunction' and 'vasomotor symptoms'. Acceptable test–retest reliability coefficients for the three subscales have been found (Greene, 1998).

Social support was assessed using the Multidimensional Scale of Perceived Social

Support (MSPSS; Zimet, Dalhem, Zimet, & Farley, 1988), which consists of 12 statements about support (i.e. 'There is a special someone who is around when I am in need'). Participants are asked to indicate the extent to which they agree with each statement based on a 7-point Likert scale ranging from 1 (Very strongly disagree) to 7 (Very strongly agree). The MSPSS is scored into 3 dimensions of support: support from a significant other, support from family, and support from friends. There is also a total support score. The MSPSS has been shown to have good reliability and moderate validity (Zimet et al., 1988).

Procedure

Ethical approval for this project was obtained from the Human Research Ethics Committees of the Alfred hospital and Monash University. Women were recruited predominantly through the Monash University community, via advertisements in electronic newsletters and posters. Several advertisements and posters were also displayed at menopause clinics, on depression websites, and at Community Health Centres. Individuals interested in participating were asked to contact the researchers via email or telephone details provided, at which point they were provided with details regarding the goals and rationale of the study and the requirements of participation. If participants indicated that they were still interested in participating, a questionnaire pack was sent out to the mailing address they provided. Included in this pack included a participant information and consent form, a series of questionnaires, and a reply paid envelope addressed to the researchers. Upon researchers receiving completed questionnaire, participants were sent a $20 gift card. Data was collected from August 2010 to February 2012.

Analysis

All analyses were conducted with IBM SPSS statistics Vs. 19. First, Pearson correlation analyses were employed to identify the study variables that had a significant univariate relationship to depressive symptoms (measured using BDI-II). Secondly, variables that were significantly associated with BDI-II scores at the univariate level ($p < .05$) were included in a multiple linear regression analysis to determine multivariate significance.

Results

Sample Characteristics

The participants had a mean age of 49.53 (SD = 4.30; range = 37-58) years (see Table 1). The majority of participants were married (57.9%) and had children (82.9%). Most had completed a postgraduate level of education (50%) and worked full or part time (46.1% and 35.5% respectively).

Table 1. Descriptive demographic statistics of sample (n = 76)

	N	%
Marital status		
Single	6	7.9%
Married	44	57.9%
De Facto	7	9.2%
Boyfriend/girlfriend	3	3.9%
Separated/divorced	14	18.4%
Widowed	2	2.6%
Children		
Yes	63	82.9%
No	13	17.1%
Employment		
Not employed	8	10.5%
Casual/contract	6	7.9%
Part time	27	35.5%
Full time	35	46.1%
Smoker		
Yes	8	10.5%
No	68	89.5%
Education		
Did not complete high school	2	2.6%
Completed high school	7	9.2%
Began university/TAFE	3	3.9%
Completed TAFE degree/diploma	7	9.2%
Completed university degree	9	11.8%
Began postgraduate degree	10	13.2%
Completed postgraduate degree	38	50%

Predictors of Depression during Perimenopause

The mean BDI-II depression score for the sample was 13.98 (S.D. = 9.72; range: 0-40). Based on a cut off BDI-II score of 13, 52.6% of the sample was considered to be in the depressed range.

To assess for univariate relationships between study variables and depression, a series of bivariate Pearson correlations were conducted (see Table 2). Positive significant relationships were found between current depression severity and history of anxiety, history of depression, history of PMS, recent negative life events, and somatic symptoms. Total social support and income were significantly negatively correlated with current depression severity. Additionally, a trend towards significance was found between increased aerobic exercise and lower depression scores (p = .083).

Table 2. Bivariate Relationships between BDI-II scores and VMS, Demographic characteristics and History of mood and hormonal disorders

Characteristic	Pearson Correlation Coefficient	Level of Significance	*N*
Education	0.02	.879	76
Total support	-0.23	.048	76
Smoking	0.08	.493	76
Aerobic exercise	-0.20	.083	76
Non-strenuous exercise	0.01	.941	76
History of Anxiety	0.25	.031	76
History of Depression	0.37	.001	76
History of Postnatal Depression	0.08	.527	64
History of PMS	-0.24	.042	75
Somatic symptoms	0.49	< .001	76
Vasomotor symptoms	0.14	.222	76
Recent Negative Life Events	0.49	.000	76

In the second step of the analysis, those variables that had a significant univariate correlation with BDI-II scores were entered into a multiple regression analysis (see Table 3). This included social support, somatic symptoms, recent negative life events, history of depression, history of PMS and income. In order to meet the multiple regression requirement of collinearity, a correlation matrix was run to check that predictors were not too closely related. History of anxiety and history of depression were found to be highly correlated (r = 0.63, p <.001). Depression had the stronger

relationship with BDI-II scores and so this predictor was retained and history of anxiety was excluded. The assumptions of normality, homoscedasticity and linearity were met. A significant regression model emerged, $F(5,69)=10.61$, $p < .001$, explaining 43.5% of the variation in depression scores (Adjusted R square = .39). Unique variance in depression scores was explained by current level of somatic symptoms, history of depression and recent life, with higher levels of each associated with higher depression severity.

Table 3. Multivariate associations of BDI-II scores

	Beta	SE B	β	t	Level of Significance
Social Support	-0.01	0.05	-0.17	-1.86	.067
Somatic symptoms	0.86	0.27	0.32	3.17	.002
Recent Negative Life Events	0.27	0.09	0.31	3.13	.003
History of Depression	4.57	1.96	0.23	2.33	.023
History of PMS	0.05	1.99	0.02	0.24	.809

Discussion

This study was designed to assess the unique association between a number of biological, social and psychological predictors and depressive symptoms during perimenopause. Three significant predictors of current depressive symptoms were found: recent negative life events, a history of depression and somatic symptoms of perimenopause.

Consistent with the stress-diathesis model of depression, the more negative life events recently experienced was related to higher reports of depressive symptoms. This is consistent with the majority of the current research, both for perimenopausal depression and for depression more generally (Bromberger et al., 2011; Cooke, 1985; Hecht & Mensh, 1975; Kendler et al., 2000; Schmidt, Murphy, et al., 2004). A higher number and severity of active negative stressors being experienced may therefore overwhelm coping resources of women during perimenopause, increasing their risk of depressive symptoms. Whether the role of life events for perimenopausal depression differs in quality or quantity to that found for standard depression is beyond the scope of this study but certainly warrants further investigation. An important factor to acknowledge is that the life events scale used was a self-report measure, which are an inherently inaccurate process (Monroe & Harkness, 2005). Several personality factors have been identified as important mediators of the effects of negative life events on depressive symptoms more generally (Kafanelis, Kostanski, Komesaroff, & Stojanovska, 2009), and it is likely that this is true in perimenopausal populations as well. It may be that feeling depressed alters the perception of the negative events one experiences, thus leading to inflated life event scores. Exploring further the link between perceived negative life events, coping ability and current depressive symptoms is therefore

important.

Additionally, more somatic symptoms were found to correlate with an increase in depression scores. The experience of somatic symptoms may be considered as both a potential stress-inducing biological event that participants were unable to cope with, and it may make the depressed person rate their somatic symptoms more highly (e.g., negative attentional bias). In fact, somatic symptoms made the strongest unique contribution to explaining depression scores, when controlling for the variance explained by the other predictors in the model. The finding that somatic symptoms were related to depressive symptoms *independently* of VMS is novel. This is further evidence that the experience of VMS is unlikely to cause a reactive depression in most women. It is, however, possible that when severe somatic symptoms are experienced, there may be a biologically stress-inducing situation that may result in depressive symptoms. The picture is complicated, however, when we consider that somatic complaints often accompany depression more generally, meaning that this relationship is not necessarily causative (Bromberger et al., 2009).

Support for a cognitive-behavioural model of perimenopausal depression can be found in the increase in depression scores for those women with a history of past depression. This finding is consistent with Bromberger et al. (2011) who found that women who experienced major depression during the perimenopausal/early postmenopausal period were nearly three times as likely to have a past history of major depression. The current study is the first to show that this relationship exists even at the level of minor depressions. A previous history of depression may be a marker of poorer coping abilities or more negative thinking styles, and subsequent increased vulnerability to stress (Lewinsohn, Allen, Seeley, & Gotlib, 1999). Clinicians treating patients who have a past

psychiatric history should therefore be mindful of this potential increased mood vulnerability, and more assertively screen for psychological distress across the perimenopausal period.

Although a history of PMS was a significant univariate predictor of depressive symptoms, neither a history of postnatal depression nor current vasomotor symptoms were related to depression scores. VMS symptoms and past mood disorders have been used as a proxy for hormonal disturbance and this has inherent limitations. It would have been helpful to have hormonal assays to allow for testing of whether an association between peripheral hormonal levels and mood existed. But without this data no conclusive comment can be made about biological influences. It has been suggested that women are often not reliable reporters when it comes to past histories of menstrual cycle related mood disorders and there is a tendency for retrospective accounts of PMS and postnatal depression to be inaccurate (Richards et al., 2006). It is important to remember that information about PMS and postnatal depressions for this study were collected via self-report on a dichotomous scale. Thus it may be that participants over or under reported their histories of reproductive-related mood disturbance.

Levels of social support were not a significant protective factor after controlling for other variables. There was a significant relationship found with depression at the univariate level, but this was not significant at the multivariate stage. The level of education was not a significant factor at either stage. These results would indicate that socioeconomic status and achievement are not protective against depressive symptoms in perimenopause. This result is inconsistent with the findings of Bernard L Harlow et al. (1999) and Choi, Lee, Lee, Kim, and Ham (2004),who had found education and SES to be associated with lower depression scores during perimenopause. The lack of

significance in the current study may be a function of the sample used, as most participants were university educated and had middle class incomes. To provide a more robust test of the impact of education, and SES, a sample that includes a broader sample is recommended. As such, interpretation of the impact of education and income must be made with caution although further research is required before their lack of contribution to depressive symptoms is dismissed entirely.

Exercise was not shown to significantly alter depression scores, at either the univariate or multivariate level. There was, however, a trend toward significance ($p=.08$), suggesting that perhaps a larger sample may show an ameliorating role for aerobic exercise on depressive symptoms during perimenopause. This would be consistent with past research that has found a relationship between perimenopausal depression and exercise (Brownson et al., 2000; Mirzaiinjmabadi, Anderson, & Barnes, 2006; Youngwhee & Hwasoon, 2008). It is important to acknowledge that differences in the types of exercise undertaken and the levels of energy expenditure were not considered in this study. Additionally, as we relied on self-reports of activity, the results are likely to have a degree of inaccuracy, with people over or under reporting their activity level and preferably controlled exercise regimes undertaken at fitness centres or in exercise physiology laboratories with a cohort of patients.

Although a significant amount of variance was explained in this model, there still remains 57% of the variability unaccounted for. It is likely that hormonal and/or genetic factors are responsible for some of the unaccounted variance. Hormone studies as well as detailed family histories could help claim additional variance. Additionally, personality factors that are known to influence depression were not considered. Future research that incorporates the role of personality traits and coping styles will likely

create a more comprehensive model.

Implications for Practice and/or Policy

The results of this study have important implications for the way in which health practitioners identify individuals at high risk of experiencing depressive symptoms during perimenopause. Specifically, this study highlights the need to use a biopsychosocial approach to assessment. Clinicians need to ask, not only about perimenopausal symptoms, but also the extent and nature of perimenopausal symptoms, about history of mood disorders, and additionally, to ask women about recent life stressors. Women presenting with high levels of somatic symptoms may in particular be experiencing associated depressive symptoms and benefit from mood screening. By identifying individuals at a higher risk, there is potential for early intervention and management that may be able to moderate depressive symptoms during perimenopause. Women with a past history of a depressive disorder may also benefit from being provided education on the increased risk of depression relapse during perimenopause and how to prevent or manage this. Again, the nature of preventative measures needs to take a biopsychosocial approach, including changes to diet and lifestyle, early engagement with support services, stress management and relaxation techniques. For women experiencing depressive symptoms during perimenopause, a number of treatment approaches could be considered. A recent review highlighted the emerging evidence for some hormone treatments in alleviating mood symptoms in perimenopausal women (Worsley et al., 2012). Some antidepressant medications (e.g. selective serotonin reuptake inhibitors) have also been found to be effective in treating vasomotor symptoms in addition to mood symptoms(Worsley et al., 2012). Psychological therapy that focuses on teaching more appropriate ways to cope with or

manage stress is likely to be an effective way to improve mood in perimenopausal women. Clinicians identifying women who are depressed during perimenopause should discuss their options with their patients and facilitate access to resources as appropriate.

Conclusions

In summary, the results of the current study confirm the importance of a biopsychosocial conceptualisation of depression during perimenopause. It was found that negative life events, a history of previous depression and experiencing somatic symptoms contribute to the development of depressive symptoms during perimenopause. In this study, factors which have previously been thought to be important determinants were not found to contribute any unique variance, such as VMS. Further exploration of this relationship is warranted.

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Declaration of competing interests

The authors declare that they have no competing interests.

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CHAPTER 5: THE ROLE OF COPING STYLES IN DEPRESSION DURING PERIMENOPAUSE

5.1 Preamble to Submitted Empirical Paper

This is the third empirical paper of the thesis and it contains an examination of the role of coping styles in the development of symptoms of depression during the perimenopausal transition, to see whether coping style is influential over and above factors that have previously been found to be associated with depression at this time.

This thesis aims to help provide a more comprehensive model of the risk of Perimenopausal Depression. Chapter 4 explored and clarified the roles of factors which have previously been investigated factors associated with symptoms of depression during the perimenopause, with the experience of somatic symptoms, past psychiatric history and more extensive recent negative life events each found to be significant unique predictors of current depression severity. This chapter adds to these findings by exploring the role of coping styles as protective or risk factors for developing depression during the perimenopause.

The aim of this study was to examine the role of personality factors in the development of depression during perimenopause. This was examined using a cross-sectional sample of perimenopausal women who were experiencing depressive symptoms and comparing them to a sample of perimenopausal women who were not experiencing depression.

This paper significantly adds to the literature because personality-related factors, which include coping style, have received little previous attention in the context of research

conducted to explore protective or risk factors for depression during the perimenopause. This has been a hereforto un-researched area in the field and provides important information that will assist in identifying women who due to their approach to coping with stress may be at risk for developing depressive symptoms. This data may also highlight potential protective approaches to coping during perimenopause that may be incorporated into psychological interventions tailored to perimenopausal women.

This article was submitted to the Australian Psychologist on 30th December 2012. *Australian Psychologist* is the official applied practice and public policy journal of the Australian Psychological Society. As such, the journal solicits articles covering current issues in psychology, the science and practice of psychology, and psychology's contribution to public policy, with particular emphasis on the Australian context. It is published by Wiley.

Monash University

Declaration for Thesis Chapter 5

Declaration by candidate

In the case of Chapter 5, the nature and extent of my contribution to the work was the following:

Nature of contribution	**Extent of contribution (%)**
Literature review, project design and writing of paper	80

The following co-authors contributed to the work:

Name	**Nature of contribution**	**Extent of contribution (%) for student co-authors only**
Dr Stuart Lee	Review of paper drafts and general supervisory input	10
Professor Jayashri Kulkarni	Review of paper drafts and general supervisory input	10

Candidate's Signature [redacted] **Date** **23/04/2013**

Declaration by co-authors

The undersigned hereby certify that:

(1) The above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) They meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) They take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) There are no other authors of the publication according to these criteria;
(5) Potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) The original data are stored at the following location(s) and will be held for at least five years from the date indicated below:
Locations(s) Monash Alfred psychiatry Research Centre

		Date
Signature 1	[redacted]	23/04/13
Signature 2	[redacted]	26/04/2013

5.3 The role of coping styles in depression during perimenopause

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Abstract

Perimenopause is a period of increased risk for depression in women. This paper examines the role of coping styles in predicting Perimenopausal Depression and investigates the role of coping styles. Seventy-six perimenopausal women who were either depressed or not depressed were recruited (M = 49.5 years; SD = 4.3). Using a cross-sectional design, participants were assessed via measures of the following variables: mood & somatic symptoms, depression history, stressors and coping styles (assessed using the Brief Cope). Univariate relationships between 14 Coping Styles and Beck Depression Inventory-II scores were assessed. Significant variables were analysed via hierarchical multiple regression which also included previously identified risk factors (somatic complaints, history of depression and negative life events). Coping styles self-blame and behavioural disengagement were significant, predicting 15% of the variance in depression scores. The positive relationship between history of depression and current depression severity was found to be mediated by use of the behavioural disengagement. Results indicate that the use of behavioural disengagement and self-blame play an important role in predicting increased depression during perimenopause. Additionally, the relationship between have a past history of depression and severity of depression during perimenopause was mediated by the use of behavioural disengagement. This has implications for how we conceptualise and treat depression clinically at this time, with a particular need to assess how women are choosing to cope with their experience of perimenopause.

Keywords Coping, Depression, Perimenopause, Risk

Introduction

Perimenopause refers to the time immediately prior to menopause, beginning with endocrine, biological and clinical changes, and ending in the year after the final menstrual period (Brambilla et al., 1994). The transition to menopause has long been considered a time of psychological turmoil, with reports of women having anywhere between 2 to 14 times the risk of depression during perimenopause (L. S. Cohen et al., 2006; E. W. Freeman et al., 2006; Schmidt, Haq, et al., 2004; Schmidt et al., 2000). The risk of becoming depressed during perimenopause has been shown to be modulated by a number of factors, including the presence and severity of physical symptoms of perimenopause, individual sensitivity to hormonal variations, as well as health and lifestyle factors (Gibbs et al., 2012 for a review).

The research literature on stress and depression more generally includes the study of biochemical and physiological factors, the impact of upbringing and trauma, cultural factors, as well as the contributions made by intrinsic personality factors, such as attitudes, thinking styles and coping strategies (Schotte et al., 2006 for a review). Looking specifically at Perimenopausal Depression, the role of personality factors and coping styles have not been adequately considered (Rostrosky & Travis, 1996). Coping refers to cognitive and behavioural strategies used by an individual in an effort to manage stressors (internal or external) that are perceived to be demanding and/or threatening (Lazarus, 1991). Adaptive coping refers to coping styles that involve efforts to remove stress, adjust the way the person thinks about the stressful situations (e.g. putting things into perspective, positive reappraisal of responsibility), and efforts to effectively manage stress reactions (e.g. relaxation techniques, increased exercise). In contrast, maladaptive coping styles tend to involve withdrawal from social supports,

aggression and exaggerated use of defence mechanisms (such as avoidance), and a lack of problem solving skills (or use of ineffective ones, such as substance use). Coping styles which have been found to lead to better psychosocial functioning include those which are behaviourally focused (e.g. increased exercise, support seeking, or relaxation strategies: Boschi et al., 2000), involve acceptance of difficulties and development of a positive attitude (Hatfield & Lefley, 1993), and are based in religion or spirituality (Murphy, 2000). In contrast, coping methods that have been found to predict poorer outcomes include behavioural disengagement, avoidance, self-blame and denial, which result in either an exacerbation of stress or only a temporary mitigation, with stress subsequently returning at an intensified level (Antoni et al., 1991; Carver et al., 1993). Research which has focused on women and coping has found consistent results, with active coping styles (i.e. those that are more problem focused and adaptive) found to be associated with higher levels of wellbeing, and avoidant coping found to be associated with lower levels of wellbeing (Kershaw, Northouse, Charuwan Kritprachab, Schafenackerb, & Mood, 2004).

From the handful of studies that have looked at coping styles during menopause, there is evidence that coping style predicts both the experience and reporting of physiological symptoms (i.e. vasomotor symptoms) as well as mood symptoms. Igarashi, Saito, et al (2000) found that the vasomotor symptoms (VMS: e.g. hot flushes and night sweats) experienced during menopause were positively correlated with the degree to which an avoidant coping style was used. In an interview-based qualitative study, Kafenelis, Konstanski, Komesaroff and Stojanovska (2009) found that how well a woman copes with stressors during the perimenopause seemed to be related to a perceived level of social integration, acceptance or isolation. This is consistent with evidence that

belonging to a community or network increases one's ability to cope and adjust to changes (Bess, Fisher, Sonn, & Bishop, 2002). Kafenelis et al (2009) found that women who were adaptively dealing with the menopausal transition focused on faith, internal strength, effective relationships with self and others, and non-judgemental engagement with the world around them. This seems to foster positive cognitive reframing of what it means to be menopausal, moving away from ideas of illness or old age, towards a more objective understanding of menopause as a natural process. This change in thinking can then lead to an increased self-awareness of how they might impact their symptoms via lifestyle and behavioural factors. This in turn leads to the use of more adaptive coping skills that encourage active coping (i.e. physical exercise, problem solving and social connection). By comparison, women who were struggling to adjust were more likely to associate menopause with feelings of anger, powerlessness, and sadness over loss of youth and vitality (Kafanelis et al., 2009). Such cognitive appraisals do not encourage adaptability, help-seeking, self-efficacy, or self-reflection, resulting in decreased proactive coping (Folkman, 1986, 1997; Folkman & Lazarus, 1985).

There is reason to believe that depression during perimenopause is influenced by psychological factors, as well as biological and social factors, and broader consideration of the extent to which each contributes to psychopathology is needed. By considering personality factors, such as coping styles, as well as biological causes of depression during perimenopause, there is potential to highlight a role for cognitive, behavioural or interpersonal interventions, in addition to pharmacotherapy. This may assist in offering a broader array of interventions that can be better tailored to the individual experiences of women during perimenopause, giving women greater choice and control over their mental health. Given the very limited body of research in this area, our research aims to

look at the relationship between various coping styles and depression during the perimenopause. A theoretical biopsychosocial model of Perimenopausal Depression aetiology includes biological causes such as the loss of neuroprotection through declining estrogen levels (Ironson et al., 2005); social causes such as experiencing difficult midlife events (Dennerstein et al., 2001; Greene & Cooke, 1980); and psychological factors (Morse, Dudley, Guthrie, & Dennerstein, 1998). We contend that coping styles remain as a significant predictor of current depression severity after accounting for other factors.

This research aims to investigate the role of coping style in whether a woman becomes depressed during perimenopause, and how this then fits in with other factors that have already been shown to predict depression at this time.

Method

Participants

This study was conducted as part of a wider project using a cross-sectional sample design. Participants were women who currently identified themselves as perimenopausal and/or as suffering from symptoms of depression. Participants were recruited predominantly through the Monash University community, via advertisements in electronic newsletters and posters. Several advertisements and posters were also displayed at menopause clinics, on depression websites, and at community health centres. Individuals interested in participating were asked to contact the researchers via email or telephone, at which point they were provided with details regarding the goals and rationale of the study and the requirements of participation. All women who were included (*N = 76)* were currently physically well, able to give informed consent, over the age of 18, were proficient in English, and were perimenopausal. Women were considered to be perimenopausal if they were experiencing irregular menstrual bleeding; if their last menstrual cycle was within the last 2 years and they continued to experience VMS (Holman et al., 2002; Mansfield et al., 2004). Forty-seven per cent of the overall sample was identified as currently experiencing symptoms of depression, based on Beck Depression Inventory II (BDI-II) scores above 13 (Beck et al., 1996). The data from participants was cleaned and screened before analysis to ensure missing data were random in occurrence and that all data was within expected ranges. Responses from 16 (18%) individuals were excluded because they did not meet the criteria for Perimenopausal status.

Procedure

Potential participants were sent a questionnaire pack was sent out to the mailing address they provided. Included in this pack were participant information and consent forms, a series of questionnaires, and a reply paid envelope addressed to the researchers. Once the questionnaires were completed, they were returned via reply paid envelope to members of the research team. Upon researchers receiving completed questionnaire, participants were sent a $20 gift card. Data was collected from August 2010 to February 2012.

Measures

Demographic variables included age, relationship status, education, their occupation and current occupational status, and their household income. Additionally, the questionnaire asked about their exercise regime, any history of past mood disorders or menstrual cycle related mood disorders.

Depression was assessed using Beck Depression Inventory II (BDI-II) (Beck et al., 1996). Participants with scores above 13 were considered depressed. The BDI-II is a 21-question multiple-choice self-report inventory, which asks how the subject has been feeling in the last week. Each question has a set of at least four possible answer choices (0-3), ranging in intensity. For example: (0) I do not feel sad, (1) I feel sad, (2) I am sad all the time and I can't snap out of it, or (3) I am so sad or unhappy that I can't stand it. The total score is then used to estimate the level of depression, i.e. minimal depression (0-12), mild depression (13-19), moderate depression (20-28), and severe depression

(29-63). This scale is one of the most widely used instruments for measuring the severity of depression. Reliability and validity of the BDI-II has been confirmed in several studies (Osman et al., 1997; Storch et al., 2004).

Coping was assessed using the Brief COPE (Carver, 1997) which consists of 14 scales which measure the degree to which different coping styles are utilized. Each scale has two items and responses are made on a 4-point Likert scale (1 – I haven't been doing this at all; 2 – I've been doing this a little bit; 3 – I've been doing this a medium amount; 4 – I've been doing this a lot). The scales and a sample item of the 14 scales of the Brief Cope are as follows: (1) Active Coping: "I've been concentrating my efforts on doing something about the situation I'm in"; (2) Planning: "I've been thinking hard about what steps to take"; (3) use of emotional support: "I've been getting emotional support from others"; (4) Use of instrumental support: "I've been getting help and advice from other people"; (5) Positive reframing: "I've been trying to see it in a different light, to make it seem more positive"; (6) Acceptance: "I've been accepting the reality of the fact that it has happened"; (7) Religion: "I've been praying or meditating"; (8) Humor: "I've been making jokes about it"; (9) Venting: "I've been saying things to let my unpleasant feelings escape"; (10) Denial: "I've been saying to myself "this isn't real."; (11) Substance use: "I've been using alcohol or other drugs to make myself feel better"; (12) behavioural disengagement: "I've been giving up trying to deal with it"; (13) Self-distraction: "I've been doing something to think about it less, such as going to movies, watching TV, reading, daydreaming, sleeping, or shopping"; and (14) Self-blame: "I've been criticizing myself". The Brief Cope has been shown to have good reliability and validity (Carver, 1997).

Recent Life Events were recorded using the Negative events scale of the Life Experience

Survey (LES)(Sarason et al., 1978), which is a questionnaire assessing the presence of 57 events (both positive and negative) that are known to be stressful (i.e. 'death of a close family member' and 'outstanding personal achievement'). If present in the last 6 months, participants were asked to rate the extent to which they viewed the events as having either a positive or negative impact on their life using a 7-point Likert scale from -3 (Extremely Negative) to +3 (Extremely Positive).

Somatic symptoms of perimenopause were assessed using the S (Somatic) of the Greene Climacteric Scale (GCS) (Greene, 1998), which is a brief checklist (21 items) providing a subjective measure of mood disturbance, hot flushes, night sweats and vaginal dryness. Only the scale which looked at the somatic symptoms of perimenopause was utilised. On the GCS, symptoms are listed and then each symptom is rated by the respondent according to its severity using a four-point scale: not at all (0); a little (1); quite a bit (2); and extremely (3). Acceptable test–retest reliability coefficients for the three subscales have been found (Greene, 1998).

Analysis

The first stage of analysis involved univariate analysis of each of the 14 scales of the Brief Cope with BDI-II depression scores. The second stage involved hierarchical regression. The first block of this regression included other factors that have been indicated in the research to be unique predictors of Perimenopausal Depression in previous research. Those scales that had a significant relationship with depression scores were then placed in a hierarchical regression in the second block.

Results

Sample Characteristics

The participants had a mean age of 49.4 years (SD = 4.33 years) with a range between 37 and 58 years. The majority of participants were married or in de facto relationships (67.1%). The majority of women had completed a postgraduate level of education (50%) and worked full or part time (46.1% and 35% respectively). Additionally, the majority of the sample (39.5%) had a combined household income above $100,000 annually (see Table 1)

Table 1. Descriptive demographic statistics of sample (N = 76)

	N (%)
Marital status	
Single	6 (7.9)
Married/De Facto	51 (67.1)
Boyfriend/girlfriend	3 (3.9)
Separated/divorced/widowed	16 (21)
Employment	
Not employed	8 (10.5)
Casual/contract	6 (7.9)
Part time	27 (35.5)
Full time	35 (46.1)
Income (AUD$)	
<20,000	4 (5.3)
21-40,000	3 (3.9)
41-60,000	10 (13.2)
61-80,000	18 (23.7)
81-100,000	11 (14.5)
>100,000	30 (39.5)
Education	
Did not complete high school	2 (2.6)
Completed high school	10 (13.1)
Completed TAFE degree/diploma	7 (9.2)
Completed university degree	19 (25)
Completed postgraduate degree	38 (50)

Coping styles and BDI-II scores

Using Pearson correlation analysis (two-tailed), the relationships between the 14 coping scales of the Brief COPE and the BDI-II depression scores were examined. The results of this univariate analysis are summarised in Table 2. The coping styles that were significantly correlated with depression severity at an alpha of .05 were behavioural disengagement, self-blame, denial, substance use, venting and self-distraction.

Table 2. Univariate relationships between Brief COPE scales and BDI-II scores (N=76)

Coping Style	Pearson's correlation (*r*)	*p*-value
Active Coping	.00	.997
Planning	.12	.292
Use of emotional support	-.01	.353
Use of instrumental support	.04	.726
Positive reframing	-.11	.346
Acceptance	.07	.517
Religion	-.01	.215
Humour	.17	.140
Venting	.27	.018
Denial	.46	<.001
Substance use	.32	.005
Behavioural disengagement	.61	<.001
Self-distraction	.43	<.001
Self-blame	.52	<.001

Coping Styles as Multivariate Predictors of Current Depression Symptoms

This analysis was performed through the use of a hierarchical multiple regression, which entered somatic complaints, history of depression and negative live events as block one. The coping styles that were significantly related to current depression at a univariate level were then entered as block 2.

Prior to conducting the analysis it was found that the assumptions of normality,

homoscedasticity, linearity and collinearity were met. The hierarchical regression analysis found that Block 1 (somatic complaints, history of depression and negative life events) predicted a significant proportion of the variance in current depression severity, $F(3,72) = 16.39$, $p < .001$, explaining 40.1% of the variation in depression scores (Adjusted R square = .38). The addition of the five coping styles that had significant univariate relationships to depression severity (behavioural disengagement, self-blame, denial, substance use, venting and self-distraction) in Block 2, significantly increased the proportion of variance in depression severity explained by the model, F change(6, 66) = 3.67, $p = .003$, explaining an additional 15% of the variance in depression scores. Tolerance statistics were between 0.4 and 0.9 for all variables, demonstrating that colinearity was not likely to bias calculation of model coefficients. As Table 3 shows, the addition of the coping styles to the model resulted in history of depression no longer being a significant predictor, whereas negative life events and somatic symptoms remained significant, positive predictors. Of the five coping styles, only self-blame and behavioural disengagement remained as significant positive predictors of depression severity.

Table 3. Hierarchical model of predictors of BDI-II scores

		Beta	SE B	β	t	*p*-value
Model 1	**Somatic symptoms**	0.94	0.25	0.35	3.71	< .001
	Negative Life Events	0.27	0.09	0.31	3.13	.003
	History of Depression	4.05	1.89	0.21	2.14	.035
Model 2	**Somatic symptoms**	0.60	0.26	0.23	2.30	.024
	Negative Life Events	0.17	0.08	0.20	2.07	.042
	History of Depression	2.25	1.86	0.12	1.22	.229
	Self-distraction	0.25	0.57	0.05	0.43	.666
	Denial	0.29	0.97	0.03	0.31	.761
	Substance use	-1.01	0.56	-0.19	-1.81	.075
	Venting	-0.46	0.61	-0.07	-0.75	.453
	Self-blame	1.51	0.58	0.27	2.60	.012
	Behavioural disengagement	2.61	0.99	0.34	2.62	.011

With both self-blame and behavioural disengagement remaining significant predictors in Block 2, and with history of depression no longer a unique significant predictor, a secondary analysis was conducted to explore whether the relationship between history of depression and current depression was mediated by a coping style. Mediation analysis was performed (As outlined by Baron & Kenny, 1986) looking at the two significant coping styles (Self-blame and behavioural Disengagement) as potential

mediating variables, with history of depression as the independent variable and BDI-II scores as the dependent variable. If a mediation relationship was present for either of these two coping styles, the relationship between BDI-II scores and a history of depression should be reduced when either behavioural disengagement or self-blame is added to the regression equation. The conditions of mediation were met for behavioural disengagement: History of depression was a significant predictor of BDI-II scores and of behavioural disengagement, and behavioural disengagement was a significant predictor of BDI-II scores while controlling for history of depression. As Figure 1 illustrates, the standardised regression coefficient between history of depression and BDI-II scores decreased substantially when controlling for behavioural disengagement. Mediation conditions were not met for self-blame, as history of depression was not a significant predictor of self-blame.

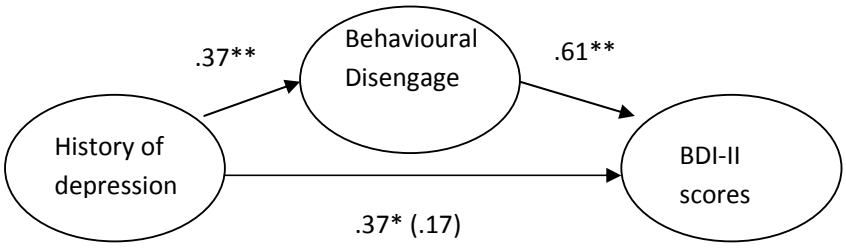

Figure 1. Path model demonstrating Behavioural Disengagements' mediation of the relationship between history of depression and current depression severity. The non-significant standardised coefficient between History of Depression and BDI-II controlling for Behavioural Disengagement is in parentheses. All other values display univariate standardised coefficients.

*$p<.05$

** $p<.01$

Discussion

The importance of coping style as either a protective or risk factor for developing depression during perimenopause has rarely been considered in previous research. The aim of our study was therefore to build on previous findings in the literature identifying a number of biological and social factors as predictors of depression symptoms, by measuring the extent to which different coping styles improved the prediction of depression during perimenopause over and above previously identified significant biological and social factors.

Analysis conducted in the current study found that five coping styles had significant univariate relationships (all positive with higher scores on each coping style associated with higher depression severity) with current depression severity: behavioural disengagement, self-blame, denial, substance use, venting and self-distraction. Of interest, all five coping styles could be considered maladaptive, whereas none of the adaptive coping styles were found to predict current depression severity. When adding these five predictors into a regression model that included negative life events, past history of depression and somatic symptom severity, previously shown to be significant unique predictors of depression severity, the addition explained a further significant amount of depression severity variance. In the final model, only negative life events, somatic symptom severity, behavioural disengagement and self-blame remained as significant unique predictors, with higher scores on each variable predictive of higher depression severity. The relationship between history of depression and current depression severity was found to be mediated by use of the behavioural disengagement

coping style.

It was not anticipated that the relationship between past depression and current depression severity would be mediated by behavioural disengagement, but this finding may suggest a role for this particular coping style in recurrent depression more generally. A previous history of depression may be a marker of poorer coping abilities or more negative thinking styles, and subsequent increased vulnerability to stress (Lewinsohn et al., 1999). As defined by Carver, Scheier and Weintraub (1989), behavioural disengagement refers to a reduction in efforts to deal with a stressor, to the point that other goals with which the stressor is interfering are also abandoned. Theoretically, behavioural disengagement is closely related to the concept of learned helplessness, which refers to passive behaviour produced by exposure to an unavoidable aversive event (Maier & Seligman, 1976). Learned helplessness can over-generalise to events where despite actually being able to exert control, the person instead accepts setbacks passively. It appears that, in this sample of women, a tendency toward behavioural disengagement as a coping style may predict a vulnerability to depressive episodes. A tendency to use behavioural disengagement may predict a lifelong vulnerability to depression, as during periods of high stress, the use of behavioural disengagement may create isolation, preventing the capacity to access social support to assist in managing the stress. Increased isolation may also result in increased ruminative behaviour, fixating on the causes of or consequences of the stressors, potentially exacerbating the depressive symptoms. Although it is beyond the scope of this paper to address causal mechanisms behind this relationship, it could be hypothesised that the stress associated with depression, in addition to the vulnerability to mood disturbance associated with the hormonal changes at this time, could result in activation of

longstanding, maladaptive coping styles, such as behavioural disengagement.

Self-blame was also shown to be a unique significant predictor of depressive symptoms. Past research has shown that self-blame is often a predictor of poor adjustment under stress (Bolger, 1990; McCrae & Costa, 1986). Referring to a tendency to assume personal responsibility for failures and negative outcomes, self-blame creates a distorted sense of actual accountability (Beck, 1967). There are significant biological changes that are experienced by women going through perimenopause and women who respond with self-blame may be more prone to depression because of the lack of control and the belief that they should be able to do more. This potentially can lead to more negative cognitions (e.g., helplessness, decrease in self-worth) that are underpinning increased mood symptoms for some women. The results of this study raise the possibility that women who felt that they were in some way to blame for their symptoms of perimenopause (symptoms that are largely out of their control) were more vulnerable to experiencing depression. For women in perimenopause who are displaying high levels of self-blame, education regarding what can and cannot be controlled regarding any biological changes, coupled with education on how a perceived lack of control can lead to the experience of negative cognitions, could serve either a preventative role or assist in treating experienced depressive symptoms.

The results of this study have important implications for how we conceptualise and treat depression during perimenopause. As certain coping styles are associated with worse outcomes, this gives therapeutic interventions a clear target to work with. The way in which an individual copes is dynamic, and the way in which an individual copes in any one instance includes complex personality, situational and historical factors (Lazarus, 1993). Increased psychoeducation about helpful and unhelpful coping styles targeted at

women entering the perimenopause may prove to be a simple, cost effective intervention for the prevention of depression at this time.

While the current findings are promising, this study had some limitations. The concept of coping is multifaceted and it is known to be dynamic, with individuals using different styles depending on the situation, resources available and their interpretation of stressors (Folkman, 1997). The results of this study need to be considered with this in mind. Additionally, the sample size was relatively small which limited statistical analyses. Larger numbers in future research would allow for more sophisticated understanding of the interactions between various coping styles, and other factors. Additionally, as this was an observational study design, it cannot be determined that the relationship between coping styles and depression scores is causal, or which factor predicts which. The coping styles that have been identified as influential in this study (e.g., self-blame and behavioural disengagement) can be broadly categorised as dysfunctional, that is to say, they have been found to be associated with poorer health and wellbeing outcomes (Carver, 1997; Carver et al., 1993; B. Meyer, 2001). For example, it is known that several of the coping styles we have identified as being related to higher depression scores are also known to be symptoms of depression, i.e., behavioural disengagement and self-blame. Therefore, it is possible that poorer coping styles are utilised by people suffering from depression, rather than poorer coping styles resulting in high depression scores.

The results of this study indicate that the use of behavioural disengagement and self-blame play an important role in the likelihood of women developing depression during perimenopause, above and beyond the impact of somatic symptoms of perimenopause and recent negative life events. Additionally, it seems that a history of depression is a

risk factor for depression only in that it indicates a tendency to use a behavioural disengagement coping style. This has implications for how we conceptualise and treat depression at this time, and offers clear targets for psychologically-based therapeutic intervention. Pharmacological interventions continue to be an important element of management of depression during perimenopause, but for many women, due to the risks associated with cancer and due to problematic side effects (Collaborative Group on Hormonal Factors in Breast Cancer, 1997; Writing Group for the Women's Health Initiative Investigators, 2002), or personal beliefs or attitudes, medication is not always a viable option. Additionally, for many women, a combination of psychological and pharmacological intervention may produce better outcomes. Either way, an increase in choices for women struggling to cope with perimenopause has the potential to improve depressive symptoms, and hopefully, an individual's quality of life.

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CHAPTER 6: INTEGRATED DISCUSSION

The purpose of this thesis was to develop a greater understanding of depression during the perimenopausal transition, including how depression symptoms present during this time, and to establish a more comprehensive model of factors associated with depression during perimenopause. Previous research in this area has not been able to provide a cohesive biopsychosocial picture of depression during the perimenopause, with inconsistent evidence regarding both causal factors and symptom characterisation. This thesis therefore focused on clarifying the contribution of risk and predictive factors for developing symptoms of depression during this time, as well as examining what differences exist in its presentation compared to depression during the childbearing years, and the subsequent implications for treatment.

This chapter includes a critical examination of the major findings from the three empirical studies that comprise this thesis. First, the findings related to the three aims of this thesis will be summarised. To reiterate, these aims were (i) to explore whether the experience of adverse mood symptoms during perimenopause is different from that experienced during childbearing years; (ii) to measure factors that are associated with increased or decreased symptoms of depression during perimenopause in a sample of Australian women; and (iii) to assess the role of personality characteristics in the development of symptoms of depression during perimenopause. Second, the implications of these findings will be discussed, including a discussion of how the findings of this research relate to a biopsychosocial model of Perimenopausal Depression. Third, the implications for prevention and treatment of Perimenopausal Depression that are derived from this research will be explored in regards to primary

health services, community health, psychological intervention, and for perimenopausal women. Finally, the limitations of the research and directions for future research will be discussed, followed by some concluding remarks.

6.1 Overview of Main Findings

In the first empirical study (Chapter 3), the nature of depressive symptoms during perimenopause as opposed to symptoms occurring during the childbearing years was examined. It was found that subtle differences existed in symptoms reported by the two populations, with perimenopausal women experiencing milder symptoms of depression, with less anxiety, increased hostility, increased sleep disturbance and increased fatigue, compared to women in their childbearing years. These differences in symptomatic profile, whilst subtle, open up the possibility of differences in the aetiology of depressive symptoms at these two life stages, possibly related to reproductive hormonal changes during perimenopause. How these differences may occur and what the implications for management and identification of Perimenopausal Depression are will be discussed later in the chapter. Additionally, what this then means for women affected, health practitioners and those working therapeutically with this group, will also be addressed.

The second study examined the relationship between a range of biopsychosocial factors and the risk of experiencing symptoms of depression during perimenopause. These factors included perimenopausal symptoms, social support, recent life events, a history of mood disorders, exercise regime, lifestyle and wellbeing. This study found that the presence of recent negative life events, a history of depression and severity of somatic symptoms were able to predict the severity of depressive symptoms. There was also a

trend suggesting a protective role of exercise. These results again have implications for women entering the perimenopause, as well as for health practitioners and community health services.

The final study examined whether consideration of the coping styles adopted by women enhanced the ability to predict the risk of depressive symptoms during perimenopause, over and above the clinical and social factors identified as significant predictors in study two. Six coping styles, each of which may be described as an unhelpful coping style, were found to be significant univariate predictors of increased depressive symptoms for women in the perimenopausal period. These were behavioural disengagement, self-blame, denial, substance use, venting and self-distraction. After entry into a multivariate model to adjust for the contribution of other coping styles, only self-blame and behavioural disengagement remained as significant unique predictors of the severity of depressive symptoms. Behavioural disengagement was also found to mediate the relationship between a history of depression and Perimenopausal Depression, highlighting the potential for this coping style to serve as a marker of chronic depression risk. These results have significant implications for mental health clinicians working with Perimenopausal Depression and offers clear targets for therapeutic intervention. The findings of the empirical analyses are considered in more detail in the context of the three research aims of this thesis.

6.1.1 Research Aim One: Exploration of the experience of adverse mood events during perimenopause in contrast to that of depressive symptoms during the childbearing years.

There has been little previous research exploring whether the depression symptoms experienced during perimenopause differ from those experienced during the child bearing years, despite speculation and anecdotal reports stretching back 100 years (Kraepelin & Diefendorf, 1907). The rise in depression rates during perimenopause, from anywhere between 2 to 14 times higher than in the premenopausal years (L. S. Cohen et al., 2006; E. W. Freeman et al., 2006; Schmidt et al., 2000), has led to the theory that the hormonal changes associated with perimenopause are causally related to this increase in depressive symptoms. As discussed in Chapter 1, it is possible that some women have a sensitivity to the normal changes in reproductive hormones associated with the perimenopause, which then creates a 'window of vulnerability', where these women are at a greater risk of depression (Soares, 2008). The proposed causative differences for depression during perimenopause, as opposed to other life stages, naturally leads to the question of whether the experience of Perimenopausal Depression is similarly different to that of depression at other stages of the reproductive life cycle (e.g., postnatal, PMS or PMDD).

The first study within this thesis aimed to quantify what, if any, differences in the experience of symptoms of depression existed between perimenopause and the childbearing years. This was conducted to assess whether presenting depressive symptoms occurring during these two life-periods differ in such a way that would support a distinction in the depressions experienced at these times. Additionally, this

study aimed to determine specifically what differences existed in symptom presentation, with the hopes the results could guide future treatment approaches.

To address these issues, the mood profiles of women experiencing symptoms of depression during perimenopause were compared with the experience of depression symptoms of women in their childbearing years. Results demonstrated that, compared to the childbearing years childbearing years, there is a distinct symptom presentation of mood symptoms for Perimenopausal Depression, characterised by milder depression and anxiety levels, increased hostility and sleep disturbance, and higher levels of fatigue that exceeds the difference expected due to increases in sleep disturbance.

These results provide confirmation of several previously identified and clinically observed features of Perimenopausal Depression, including the milder presentation (Bromberger et al., 2003; Dennerstein et al., 1993a), increased hostility (Bromberger et al., 2003; E. W. Freeman et al., 2008), fatigue (Schmidt et al., 1997) and sleep disturbance (Brugge et al., 1989; Moline et al., 2003). It is somewhat unexpected that anxiety levels are not different between the two groups of women. In a cross-sectional study, Tangen and Mykletun (2008) found higher levels of anxiety during perimenopause compared to women in the childbearing years. Additionally, Bromberger et al. (2013) found that there was an increase in anxiety symptoms in women who had low anxiety levels premenopausally, and that women with high level premenopausally continued to have high anxiety during perimenopause. Differences in the designs of these two studies, may explain the observed differences from the findings presented in Chapter 3. Tangen and Mykletun (2008) used a sample of perimenopausal women who were not necessarily depressed, and Bromberger et al. (2013) examined anxiety

specifically, and did not look at this in relation to comorbid depression. The contrast between the results of this study and the work of others suggests that whilst anxiety might be higher in perimenopausal women generally, it does not seem to be associated with Perimenopausal Depression.

The increased hostility and irritability this study found in Perimenopausal depression, as opposed to depression in the childbearing years, is consistent with the work of Bromberger et al. (2003) and with anecdotal reports (Schmidt et al., 1997; Worsley et al., 2012) but is inconsistent with the work of Kornstein et al. (2010), who found that irritability was increased during the premenopausal years. However, differences in methodology, specifically in the criteria used to assess menopausal status (i.e.age, menstrual bleeding patterns or hormone levels), may explain these differences.

This study provided clarification regarding the differences in the experience of Perimenopausal Depression as compared to the experiences during the childbearing years. In doing so, this paper adds further evidence for the hormonal theory of Perimenopausal Depression, as the subtle differences in symptom presentation raise the possibility of slightly different causal mechanisms for depression symptoms at this time. These results have implications for assessment and treatment of depression symptoms, both pharmacological and psychological, during perimenopause. Additionally, this study provides justification for further research investigating the role hormones play in the presentation of depression during this time. These implications will be discussed at greater length later in this chapter.

6.1.2 Research Aim Two: What factors are associated with increased or decreased risk of depression during perimenopause in a sample of Australian women?

While it has previously been highlighted that there is an increased risk of developing first-onset depressive disorders or relapses of depressive disorders in perimenopause, most women do not develop a major depressive illness during this time. Identifying factors that offer protection against the onset of depressive symptoms during perimenopause, or otherwise increase the risk, is an important aim of this thesis. Through communicating information about these factors to women and health professionals treating women experiencing perimenopause, interventions can be implemented to prevent or reduce the severity of depressive symptoms. This therefore formed the focus of Chapters 4 and 5 of this thesis, which report on findings detailing the role and overall contribution of risk and preventative factors in a sample of currently perimenopausal women.

There are currently many conflicting studies regarding the contribution of various factors towards the development of depression symptoms during perimenopause with little general agreement amongst the research field. Factors that have been more consistently identified as predictors include a previous history of PMS, previous history of depression, life stress, and physiological symptoms of perimenopause. The extent to which these factors can predict Perimenopausal Depression has been unclear, and a comprehensive biopsychosocial model of how these factors relate to one another is a gap in the field. The lack of an integrated theoretical framework that incorporates each of these factors has been a barrier to understanding, and therefore treating depression during perimenopause.

The second study in this thesis, reported in Chapter 4, addressed the role of various self-reported biological, lifestyle and social predictors of the severity of depression during perimenopause. This was achieved by testing whether a perimenopausal woman's level of depressive symptoms could be predicted using a variety of biopsychosocial factors. In this sample of Australian women, the only factors which were able to uniquely predict increased risk of depression were a history of depression, level of somatic symptoms, and negative life events, which explained nearly 40% of the variance in depression scores. There was also a trend towards a protective role of aerobic exercise, but this did not reach significance. As argued in Chapter 1, the identified factors associated with Perimenopausal Depression severity could be described as representing different mechanisms by which depression risk could be increased. For example, the experience of somatic symptoms could be a marker of a shared biological mechanism that is driving both the mood and physiological symptoms, or could act as a stressor (related to the stress-diathesis model) that could trigger or exacerbate mood symptoms. Similarly, the increase in depressive symptoms in the presence of more recent life events reflects the stress-diathesis model.

The significant predictors identified in this research were somatic complaints, history of depression and negative life events. Previous research has similarly found that somatic symptoms are predictive of depression during perimenopause (Bromberger et al., 2009). Somatic complaints were identified as the strongest predictor of depression scores, possibly as a result of underlying biological mechanisms, or because of the stress associated with increased somatic symptoms. Additionally, it may be that women experiencing higher levels of depression are more likely to over-report somatic

symptoms (e.g. negative attentional bias). Past history of depression has similarly been found to be predictive of depression during perimenopause (Avis et al., 1994; L. S. Cohen et al., 2006; E. W. Freeman et al., 2006). It was theorised that a previous history of depression may be a marker of poorer coping abilities or more negative thinking styles, and subsequent increased vulnerability to stress. Finally, a history of recent negative life events has consistently been found to be associated with depression during perimenopause (Bromberger et al., 2011; Cooke & Greene, 1981; Greene & Cooke, 1980), which was once again validated in this study.

With respect to the reproduction hormone depletion theory of Perimenopausal Depression, no predictive value for past history of PMS or vasomotor symptoms was found. Both these factors have independently formed the crux of two of the main theories of Perimenopausal Depression. The lack of predictive power of VMS in predicting Perimenopausal Depression is in contrast to the work of others who have found a relationship between the two (L. S. Cohen et al., 2006; E. W. Freeman, Sammel, & Liu, 2004; Joffe et al., 2002). The results of this study are more in line with the work of Ozturk et al. (2006), who did not find a relationship between the severity of VMS and Perimenopausal Depression. Several studies have found that VMS are more strongly related to perimenopausal status, whereas psychological symptoms are more related to stress (Binfa et al., 2004; Bromberger et al., 2009; Hardy & Kuh, 2002). The lack of predictive power of a past history of PMS, postnatal depression or PMDD is inconsistent with the work of Richards et al. (2006), who found higher than expected rates of PMS, postnatal depression and PMDD in Perimenopausal Depressed women. Similar results have been reported in several other studies (Dennerstein et al., 1993a; Bernard L Harlow et al., 1999; Stewart & Boydell, 1993). The results of study two are

more consistent with the work of Schmidt, Haq, et al. (2004) or of Ozturk et al. (2006), who did not find a relationship between PMS, PMDD, or postnatal depression and premenopausal depression.

The lack of predictive power of PMS/PMDD in this research may indicate a difficulty with study designs. Research has suggested that women are not reliable reporters of PMS or PMDD, and there is a tendency for inaccuracy in self-report (Richards et al., 2006). The questionnaire used in this study asked women to report 'yes' or 'no' to a past history of PMS or PMDD and it is likely that this was based on self-reflection and not on any official diagnosis. Whilst this may be a good reflection on the incidence of mood disturbance related to menses, it is possibly not a good indicator of whether this disturbance reached a diagnostic threshold. Schmidt, Haq, et al. (2004), however, found similar results using clinical interviews. Using a cross-sectional retrospective design analogous to that employed in this thesis, Ozturk et al. (2006) found no relationship between PMS or postnatal depression and Perimenopausal Depression. As no direct hormonal assay was conducted, a hormonal explanation cannot be discounted. Rather, the utility of using PMS/PMDD or VMS as proxies for hormonal disturbance can be questioned. It seems that whilst Perimenopausal Depression and VMS often co-occur, it may be more reflective of a common underlying endocrine sensitivity than a direct causal relationship. Given the methodological issues surrounding PMS/PMDD identification, further investigation is required before their predictive power can be fully discredited.

This study was able to identify several factors associated with depressive symptoms during perimenopause, and subsequently, identifies targets for intervention.

Additionally, factors that have previously been thought to be important determinants were not found to contribute any unique variance. Results also suggest a potential role for aerobic exercise in prevention of Perimenopausal Depression, and further exploration of this relationship is warranted. The limitations of this study are addressed later in this chapter.

6.1.3 Research Aim Three: What is the role of personality characteristics in the development of depression during perimenopause?

As argued previously, a lack of an integrated model for Perimenopausal Depression that considers biological, cognitive-behavioural or stress vulnerability factors, may be limiting the potential for health professionals to understand and treat depressive symptoms during this life-stage. In addressing research aim two, previously reported biological and social predictors of depressive symptoms in perimenopause were assessed for their predictive value. Other personality or coping factors were not included. This was because the role of intrinsic psychological factors in the development of Perimenopausal Depression had not been investigated in previous research. Given the role of personality factors in depression during other life stages, and consistent with cognitive-behavioural models of depression, it is reasonable to assume that the way a woman copes with perimenopause, and the symptoms she experiences, will impact how she functions at this time. From a prevention perspective, understanding coping factors that are associated with increased risk will allow the identification of potential targets for intervention, as aspects of personality and the use of certain coping strategies can be enhanced through therapy (Grey et al., 1998; Rubin, 1993).

Coping styles have been shown to effect outcomes (both physiologically and psychologically) for the progression of diseases such as cancer (Carver et al., 1993) and HIV (Ironson et al., 1994; Kiecolt-Glaser & McGuire, 2002). It is thought that the effect of positive coping on disease outcome is mediated through a combination of factors, including: behavioural (e.g. proactive coping), cognitive (e.g. self-blame or avoidant coping), and affective (e.g depression resulting from maladaptive coping styles: Ironson et al., 2005). Specifically looking at perimenopausal symptoms, coping style may impact the use of behavioural strategies for reducing symptoms (i.e. increased exercise for reducing VMS and social connectivity improving mood); of cognitive strategies (i.e. conceptualising symptoms of perimenopause as a reprieve from the hassles of menstruation rather than as a marker of old age); and of affective strategies (i.e. being able to create distance mentally from mood symptoms related to perimenopause, such as irritability or depression, thus allowing objectivity and improved emotion regulation).

Findings presented in Chapter 5 identified that the use of particular coping styles were predictive of depressive symptoms in perimenopausal women. The two styles associated with depression symptoms were self-blame and behavioural disengagement. Both self-blame and behavioural disengagement have been found to be poor predictors of adjustment to stressors (Bolger, 1990; McCrae & Costa, 1986). Additional analysis showed that the use of a behavioural disengagement coping style mediated the relationship between history of depression and current depressive symptoms.

The role that was found for self-blame in Perimenopausal Depression raises the possibility that women who felt that they were somehow responsible for their perimenopausal symptoms were more vulnerable to experiencing symptoms of

depression. There are significant biological changes that are experienced by women going through perimenopause, including decreased energy and motivation, irritability and other mood disturbance. To provide a context for interpreting these findings using the cognitive-behavioural model of depression, the way people think (e.g., cognitions) about a particular situation can influence their resultant emotional state, physiological reaction and behaviour (Beck, 1979). Negative cognitions (such as self-blame) in response to an event can worsen the subsequent mood experience. Women who respond with self-blame, who perhaps feel cross at themselves for being less productive, for being more irritable with loved ones or for not 'snapping out' of these moods, may be more prone to depression due to a corresponding increase in negative cognitions (e.g., helplessness, guilt, decrease in self-worth).

The significant predictive role of behavioural disengagement that we found is consistent with coping research and research on depression more generally (Maier & Seligman, 1976). This suggests that women either do not believe that there are social supports available to them when encountering difficult situations, or otherwise have a preference to become isolated at this time. A benefit of engaging with others when encountering stressful situations is the ability of others to challenge unhelpful cognitions or to provide support to reduce the perception of stress (Hogan, Linden, & Najarian, 2002). When women who are vulnerable to mood disturbance are socially isolated during perimenopause, it may be that it becomes difficult for them to identify and challenge negative cognitions, resulting in a strengthening of negative cognitions that can then go on to underpin depressive symptoms. Additional analysis showed that the use of the behavioural disengagement coping style mediated the relationship between history of depression and current depressive symptoms, highlighting that this coping style may be

associated with chronic depression risk.

Findings presented in Chapter 5 identified the importance of a woman's coping styles in the development of depression during perimenopause. Additionally, it seems that a history of depression is a risk factor for Perimenopausal Depression because it indicates a tendency to use a behavioural disengagement coping style. This has implications for how we conceptualise and treat depression at this time, and offers clear targets for psychologically based therapeutic intervention. This will be discussed later in this chapter.

6.2 Implications

6.2.1 Implications: Perimenopausal Depression

Findings presented in this thesis have shown that the experience of depressive symptoms during perimenopause is subtly different from that during the childbearing years. Although the research in this thesis is unable to confirm a role for endocrine factors in the different presentations, largely due to measures of peripheral or central hormonal levels not being collected due to the study design, it can be speculated that the different presentation belies different causation. The clarification of the differing presentation of Perimenopausal Depression offers validation of the observations others have made about its unique nature (Schmidt et al., 1997; Worsley et al., 2012), which should be reassuring not only to researchers and doctors, but also to the women who suffer from this syndrome.

In addition to clarifying the symptom profile of Perimenopausal Depression, the results of this research have added to the body of work looking at a causative model. The

research in this thesis indicated that Perimenopausal Depression is best suited to conceptualisation in a biopsychosocial model. The predictive model of Perimenopausal Depression illuminated by this thesis highlights a role for psychological factors, somatic symptoms, and for the role of stressful life events. It seems important that future research should measure hormonal levels to assess in greater detail the nature and extent of hormonal contributions to this disorder.

A role for biological factors in Perimenopausal Depression has consistently been validated by research, although the exact nature of this role remains unclear. The research presented in this thesis has indicated that somatic symptoms of perimenopause are related to depressive symptoms, whereas VMS are not. This is inconsistent with research which has found a relationship between VMS severity and depression (L. S. Cohen et al., 2006; Joffe et al., 2002). It is, however, consistent with the work of Bromberger, et al. (2009) who found that a more symptomatic perimenopausal transition was associated with depression at this time. Additionally, Igarashi et al., (2000) have similarly not found a relationship between VMS and depression. Given the significance of somatic complaints as a predictor of depression (as found in chapter 4), it still seems likely that underlying biological mechanisms are in some way related to depression during perimenopause. This inconsistency may indicate that it is more likely that depressive symptoms are not caused by VMS, and are instead their co-occurrence represents a common mechanism. Specifically, there may be biological changes that underpin both VMS and mood disturbances, particularly when coupled with other vulnerability factors (e.g. coping) and stressors (e.g. more severe negative life events).

In regards to social factors, the role of negative life events was again validated as a

causal factor for Perimenopausal Depression. Consistent with the findings of this research, negative life events have previously been shown to predict Perimenopausal Depression (Cooke, 1985; Cooke & Greene, 1981; Dennerstein et al., 2001; Greene & Cooke, 1980). This finding is consistent with the idea of a 'window of vulnerability' for women during this time. Whilst these women may have previously been able to cope well with stress, during this period of increased vulnerability, potentially related to the experienced hormonal changes which are characteristic of perimenopause, additional life events may overwhelm their resources and result in depression.

The association between coping styles and symptoms of depression demonstrated the important role of psychological factors. For women prone to self-blame, they may experience the symptoms of perimenopause as being reflective of personal weakness, rather than symptoms of physiological changes. Women adopting behavioural disengagement as a coping style may then isolate themselves more when experiencing stress associated with the changes, potentially increasing the likelihood of the negative cognitions and associated depressive mood states becoming entrenched. While this research has been able to show an important role for psychological variables in the experience of perimenopause, this is only the beginning for research in this area. Further targets for research include looking at the role of positivity, as well as personality factors, such as neuroticism, in the development of Perimenopausal Depression.

When looking at what contributes to this 'window of vulnerability', the most likely factor seems to be hormonal changes that take place at this time. The social changes which were previously thought to underlie mood change and formed the basis of the 'empty nest' theory (e.g., leaving home of children etc) no longer occur in the same

way. While further research is needed, hormonal and biological changes that are associated with an array of somatic and neurotransmitter changes may underpin this window of vulnerability. This may occur both via a primary mechanism, such as altered mood-related neurotransmitter functioning, but also via a secondary mechanism through the onset of somatic changes that are distressing. Overall, the findings of this thesis produce a picture of perimenopause as a period of increased vulnerability for a woman, which is mediated by the severity of physiological symptoms, lifestyle, coping and stress. This biopsychosocial model is significant in that it offers multiple targets for intervention, including behavioural, pharmacological and psychological targets.

6.2.2 Implications: Primary care, community outreach and assessment

Primary care physicians are able to play an integral role in a woman's education about their perimenopausal transition and is, more often than not, the primary source women turn to when seeking information on this subject. Whilst education around pharmacological interventions and physiological symptoms is often of a high standard in Australia, education around the distinct nature of mood complaints during the perimenopausal transition is less clear, probably as a function of the lack of clarity about the research outcomes. Result presented in this thesis have provided key information that needs to be conveyed to women presenting to their General Practitioner for complaints related to perimenopause. Information about risk, the impact of lifestyle & wellbeing, and what indicators to look out for, needs to be conveyed to women.

Assessment of Perimenopausal Depression remains unstructured. Currently, General Practitioners and specialists rely on assessment tools relating to perimenopausal symptoms (e.g. GCS: Greene, 1991) or ones that assess depression broadly (e.g. BDI:

Beck et al., 1996) and no targeted screening for Perimenopausal Depression is widely used. The findings of this thesis suggest the need for specific assessment tools that can assist identifying Perimenopausal Depression and allow treatment. One recently developed measure which may offer more targeted assessment of depression in the perimenopause is the MENO-D, which is 12-item rating scale that includes questions regarding affective, cognitive, and physiological symptoms (Kulkarni, 2010). Further tools that are able to *predict* who is at risk of Perimenopausal Depression would allow for additional preventative measures to be taken, such as making lifestyle changes.

Although the role of pharmacological interventions is beyond the scope of this thesis, the results of these studies point toward an integrative treatment model of Perimenopausal Depression. Current research into the role of various pharmacological interventions have shown promising results, particularly for HRT based therapies (See Worsley et al., 2012 for a review: Appendix A). But there remains no 'cure all' medical intervention for the symptoms of Perimenopausal Depression. The results of research presented in this thesis, particularly Chapter 5, indicate that best practice may need to evolve to incorporate psychological intervention, in addition to lifestyle and pharmacological management.

6.2.3 Implications: Therapeutic intervention

A review of the current literature on perimenopausal depression was not able to identify any evidence-based psychological interventions tailored for women experiencing depression during perimenopause. There has been some suggestion of a role for interpersonal therapy (Banger, 2002), but no research has been done to date. This represents a significant gap, one that has already been addressed for postnatal

depression (Milgrom, Negri, Gemmill, McNeil, & Martin, 2005) and for PMS (Mussher, Hunter, & Cariss, 2002), both of which have been shown to be amenable to evidence-based psychological intervention. This lack of attention given to Perimenopausal Depression seems related to the lack of consensus as to its cause, and indeed, even to its existence.

Results presented in this thesis have provided information that can contribute significantly to the psychoeducation involved in Perimenopausal Depression treatment. Addressing both the cognitive-behavioural and stress-diathesis models, psychoeducation about the mood and somatic symptoms identified in Chapter 2 that can occur during perimenopause could serve to normalise the experiences of perimenopause. This could potentially decrease self-blame and other negative cognitive reactions that women can experience at this time. Promoting more positive adaptive coping strategies would also be helpful. Psychoeducation, delivered via General Practitioners, community centres, and via perimenopausal foundations, has the opportunity to provide women with information about what they might experience, which factors increase their risk of experiencing these symptoms, at what point they should seek help for their symptoms, and additionally, where to get help and what options for help exist. Early intervention with any mental illness offers opportunity for prevention of symptoms.

Understanding one's experiences is an important component of any intervention and there is evidence that psycheducational groups can reduce depressive symptoms in women suffering from postnatal depression (Honey, Bennett, & Morgan, 2002). In postnatal depression research, support group interventions have been shown to be an effective way to help women cope and there is reason to believe the same would be true

for perimenopausal women. Whilst support groups do exist, they are scarce and certainly not widely promoted. Anecdotal reports from participants in this research have suggested that the need for social and community supports at this time is high and mostly unmet. Although a univariate effect of social support was found in Chapter 4, this did not remain significant when accounting for other factors. Social support was measured by looking at the subjective degree of support from significant others, family and friends, but what this support consisted of was not examined. It is likely that the *kind* (or quality) of support a woman receives is more important than the amount and source of the support. A supportive group of peers struggling with similar issues is able to provide a normative function that is perhaps hard to find elsewhere, particularly within a heterosexual relationship.

Results presented in Chapter 5 may also provide valuable targets for psychological intervention. As discussed previously, the negative outcomes associated with behavioural disengagement and self-blame in perimenopausal women provide clear targets for intervention. From biological and stress-diathesis perspectives, in addition to the protective role of coping cognitively and behaviourally, there is evidence that psychological variables can impact on disease history through effects on the immune and endocrine systems (See Kiecolt-Glaser & McGuire, 2002 for a review). Although beyond the scope of this thesis, the relationship between mood and endocrine function is likely to be bi-directional, as some research has already shown (Igarashi et al., 2000). By addressing unhelpful coping styles (identified in Chapter 5) in therapy, there is an opportunity to reduce stress levels and thus potentially reduce physiological symptoms. Additionally, relaxation or mindfulness approaches can also help to enhance women's capacity to cope with stress by reducing physiological responses during this period of

vulnerability (R.Y.T, 2004).

Given the potential for multiple causal and maintaining mechanisms in Perimenopausal Depression, a treatment approach that concurrently addresses the biological and cognitive drivers of depression would be the most efficacious. For example, a pharmacological intervention that considers hormonal approaches to address both the physiological and mood symptoms of hormone changes, in addition to a cognitive behavioural therapy to address thoughts and behaviours, and relaxation training to reduce physical distress, could potentially offer the most effective treatment.

6.2.4 Implications: Women and their experience of perimenopause

The experience of perimenopause is different for every individual and the vast majority of women are able to navigate this time with little effort, and without encountering persistent or severe depressive symptoms. For a minority though, an increased understanding and awareness of their symptoms as well as the potential causes offers valuable opportunity for insight and may also serve as a motivator for change. As research continues to highlight the role of behavioural and lifestyle factors in wellbeing during perimenopause (as evidenced in Chapters 4 & 5), the role a woman can play in managing her symptoms is broadened. The impact that such knowledge can have on a woman's self-efficacy can potentially moderate their distress at this time. These factors are especially relevant when considering the relationship between self-blame and behavioural disengagement in Perimenopausal Depression, as shown in chapter 5.

6.3 Limitations and Future Directions

The primary limitation of this study relates to the sample. The sample size was modest

which limited the statistical analyses and inferences that could be drawn from the data. Larger numbers in future research would allow for more sophisticated understanding of the interactions between factors, and would more robustly assess the strength and consistency of these interactions.

Whilst the results of this study are promising, an observational study design limits the conclusions that can be drawn and no conclusions about causation can be inferred. Past history of PMS and other mood disturbance relied on self-report and it has been shown in previous studies that this is often not a reliable method (Richards et al., 2006). It has been suggested by Schmidt, Haq, et al. (2004) that the only way the relationship between hormone related mood disturbance and Perimenopausal Depression can be conclusively assessed is by using longitudinal prospective designs that use appropriate diagnostic and symptom rating measures. A possible approach for future research would be to conduct longitudinal, cross-sectional assessments to see whether the phase of perimenopause impacts on the predictive value of risk factors. This would also provide an assessment of stability of predictors over time. Cohort studies that follow women from premenopause to postmenopause are also important for helping to illuminate factors in women with no depression history but who experience a first-onset during perimenopause. This data could then be paired with intervention studies that test and compare different approaches to psychological or drug treatments.

Additionally, although care was taken to check perimenopausal status via symptom checking, determination of status relied predominantly on self-report. Ideally, future research would conduct hormonal assays to clarify a woman's perimenopausal status. Due to the substantial cost, both financially and to participants, hormonal assays were

not a viable option for this thesis. Hormonal assays would also be able to further clarify the role of female hormones in Perimenopausal Depression and allow causal relationships to be determined.

Given the inherent problems associated with self-report, it is unclear to what extent self-reported statements of frequency, amount and type of exercise undertaken were accurate. As such, it was felt that exercise was poorly captured in the current studies. Past research looking at the role of exercise in mood has shown that the nature of effects are dependent on the intensity (Thurston, Joffe, Soares, & Harlow, 2006) and amount of exercise (Morse et al., 1998; Youngwhee & Hwasoon, 2008). A more robust measure of exercising habits that can more sensitively measure frequency and intensity is required to provide a clearer indication of whether (and how) aerobic exercise may play a protective role for Perimenopausal Depression.

An important direction for future research relates to lifestyle factors and their ability to ameliorate perimenopausal symptoms. The trend for a protective role of aerobic exercise found in Chapter 4 is one that certainly warrants further attention, given the ease and accessibility of exercise as an intervention for Perimenopausal Depression. Additionally, cigarette smoking and diet may be further able to predict likelihood of Perimenopausal Depression. As discussed in Chapter 2, there is evidence to suggest that smoking and higher BMI is associated with more symptomatic perimenopausal transitions (Avis, Crawford, & McKinlay, 1997; Gold et al., 2004; Bernard L Harlow et al., 1999; Whiteman, Staropoli, Benedict, Borgeest, & Flaws, 2003). A lifestyle approach to managing perimenopause would be cost effective, have numerous other health benefits, and would offer an alternative to pharmacological intervention.

Whilst the results contained in this thesis have shown an important role for psychological factors in Perimenopausal Depression, we are perhaps only just beginning to understand the role such variables play. The role of positivity (e.g. constructs such as optimism, and finding meaning) and personality factors have been shown to impact disease progression in HIV(Ironson et al., 1994; Taylor, Kemeny, Bower, Gruenewald, & Reed, 2000) and cancer research (Carver et al., 1993) and there is good reason to believe that, through enhancing the ability to manage distressing physiological or physiological symptoms, similar results may be found in the case of Perimenopausal Depression.

The role of pharmacological interventions is beyond the scope of this thesis although a review for which I am a co-author and provides a detailed discussion about this is included as an appendix to this thesis (Appendix A). The results of the research presented in this thesis point toward an integrative treatment model of Perimenopausal Depression that considers both pharmacological (e.g. hormone replacement therapies) and psychological approaches to treatment, potentially combined for the more severely depressed patients. The research in this thesis has identified several key targets for psychological and social intervention. Future research can build from here to look at creating and shaping these interventions, in the form of educational materials, support groups and psychological treatments.

6.4 Conclusion

Research presented in this thesis provides further evidence in support of Perimenopausal Depression being a unique syndrome that is symptomatically distinct from depression

during the childbearing years. Chapter 3 showed that compared to depressed women of childbearing age, perimenopausal women were found to experience milder depression, less anxiety, with increased anger, fatigue, and sleep disturbance. Although more research is needed, these results begin to address the need for clarification of a long debated diagnosis, as well as offering targets for intervention and creating avenues for potential management.

Factors that contribute to an increase or decrease in the risk of depressive symptoms during perimenopause were also assessed in this thesis. Regarding risk, the results in Chapter 4 of this thesis confirm the role recent life stressors, past experience of depressive or anxiety symptoms and the severity of somatic complaints may play in increasing the risk of experiencing depression during perimenopause. Additionally, this research found further evidence questioning the role of VMS and of other reproductive event related mood disorders in predicting Perimenopausal Depression.

The significance of coping style in predicting symptoms of depression in perimenopause was also highlighted in Chapter 5, particularly the role of behavioural disengagement and self-blame coping styles. Additionally, it seems that a history of depression is a risk factor for Perimenopausal Depression because it indicates a tendency to use a behavioural disengagement coping style. For women entering perimenopause, awareness of their coping style and their expectations with respect to their experience of perimenopause is important information that may allow them to moderate their thoughts and behaviours (i.e. being aware of self-blaming and behavioural disengagement) to either prevent the onset of depression or treat existing symptoms. For clinicians treating perimenopausal women, even when the patients do not initially present with mood

issues, routine assessment of psychological distress should form a part of treatment practice, particularly in women displaying a past psychiatric history or multiple or severe somatic symptoms. Screening approaches for unhelpful coping styles to identify at risk women early in perimenopause may also be of value. Once depression during perimenopause is identified, pharmacological, cognitive and behavioural interventions that are tailored to the likely causes of the presenting depression symptoms for each individual should produce the best outcomes. The results in this thesis have important implications for how we educate women about perimenopause, how we identify those at risk and how we might prevent it, as well as highlighting targets for intervention, be they biological, psychological or social.

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Appendix A:

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Review

Hormonal therapies for new onset and relapsed depression during perimenopause

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ABSTRACT

In recent years the perimenopause has become recognised as a 'window of vulnerability' for women's mood. The risk of depression during perimenopause is high and treatment failure is common. Perimenopausal depression encompasses both new onset (first episode) depression occurring during perimenopause as well as a relapse during perimenopause in women with a history of depression. Perimenopausal depression is increasingly recognised as a new subtype of depression with specific clinical characteristics. Current treatments for perimenopausal depression have high failure rates, multiple adverse effects and potentially damaging long term consequences. This review examines both new onset and relapsed depression during perimenopause, biological mechanisms of perimenopausal depression, and the role of hormonal therapies.

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The perimenopause is defined as the time immediately prior to menopause, beginning with endocrine, biological and clinical changes, and ending 12 months after the final menstrual period [1]. Perimenopause is diagnosed clinically on the basis of varying menstrual cycle lengths, but is also characterised by classical menopausal symptoms including hot flushes, sleep disturbance and vaginal dryness [2]. The perimenopause, which has a median age of onset of 47.5 years [3], has distinct endocrine characteristics, with early perimenopause being a period of high gonadotropin (follicle

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stimulating hormone (FSH) and luteinizing hormone (LH)) levels and increased estradiol secretion. In contrast, later perimenopause is a time of high FSH levels and decreased estradiol secretion [4].

During the menopause transition 1 in 4 women experiences severe vasomotor symptoms (hot flushes and night sweats) and 1 in 3 experiences severe psychological symptoms (depression, anxiety) [5]. Symptoms can be severe and last for many years. Women who experience early severe vasomotor or psychological symptoms, that is, onset of bothersome symptoms up to 3 years before the menopause, are more likely to experience diminution of their symptoms by their 4th postmenopausal year, whereas women with later onset severe symptoms are more likely to have symptoms that persist for several years [5].

Whilst it is well known that depression is more common amongst women than men [6], there is now mounting evidence that the perimenopause is a time of increased risk for the onset of depressive symptoms and depressive disorders in women [7–9]. The current first line pharmacological therapy for depression is a selective serotonin reuptake inhibitor (SSRI) [10]. SSRIs undoubtedly play a very important role in the management of depression, and are considered first line therapy by most experts [11].

Unfortunately, SSRIs are not a panacea for the treatment of depression. Approximately 50% of patients will either fail to respond or only partially respond to an SSRI [12,13]. Discontinuation of antidepressants after treatment initiation in clinical practice as opposed to research settings has been reported to be 42.4% at one month and a further 30% by three months [14]. Further, evidence is emerging that SSRIs decrease bone mineral density [15,16]. This is of particular concern as it has also been shown that depressed perimenopausal women have lower bone density at the hip compared with their non-depressed counterparts [17], at a time when bone loss accelerates in women [18].

Another side effect of SSRIs of particular relevance to perimenopausal women is sexual dysfunction. As many as 50% of all women on SSRIs experience sexual dysfunction [19]. Female sexual dysfunction is associated with reduced mood, lower quality of life, relationship difficulties and discontinuation of therapy [20].

Given the need for adjunctive and alternative treatments in this group, the aim of this paper is to examine the possible utility of hormonal treatment for depression in the perimenopause by reviewing the current literature to establish: if there really is strong evidence of a connection between the perimenopause and an increase in depressive symptoms; if there is evidence to support an underlying endocrine mechanism that could explain such a relationship; and if there is clinical trial data to support the use of hormone therapy in this group. This review will not discuss the management of menopausal symptoms or depression in general.

1. Methods

There is no DSM-IV definition of perimenopausal depression per se and the terminology can be confusing. Epidemiological studies measure depressive symptoms using rating scales such as the Centre for Epidemiologic Studies Depression Scale (CES-D), whilst a diagnosis of a depressive disorder such as major depression is made clinically via a structured clinical interview. The term depression is often used as an umbrella term encompassing both 'depressive symptoms' and depressive disorders.

Hence, PUBMED was searched for English language papers using combinations of the words perimenopause, perimenopausal, depression, depressive disorder, major depression, symptoms, symptomatology. The search 'SSRI and menopause' was performed using the limits 'human, women, aged 45–64'. The MeSH terms perimenopause, depression, depressive disorder were also used. PSYCH Info was searched using the terms perimenopause and depression, perimenopausal depression. Bibliographies were also searched to find additional references. Abstracts were reviewed by one author (RW) to find original research articles. Articles concerning non-pharmacological or complementary therapies were excluded for the purposes of this review.

2. Results

In total, 70 original research articles were found, of which the key articles are presented below.

2.1. Prevalence

Thirty-two papers were found that examined the prevalence of depression during the perimenopause in both community and clinical populations. Earlier studies were somewhat equivocal [21], whilst recent studies have provided more convincing evidence of a link between an increase in depression during the perimenopause across different ethnic and cultural groups [22]. The most dramatic increase in risk of depression was seen a study of 29 women who were assessed with clinical interviews for 5 years or until they had experienced 6 months of amenorrhea. In this group, a woman's risk of an episode of major depression during the perimenopause was elevated 14 fold when compared to her risk when premenopausal [23]. Larger, longitudinal studies documenting an increase in depression during the perimenopause include the Study of Womens Health Across the Nation [24], the Penn Ovarian Ageing Study (POAS) [8] and the Harvard Study of Moods and Cycles [7]. This association has also been demonstrated in large longitudinal and cross-sectional studies outside of the United States such as the HUNT-II study which included over 19,000 women [9]. These larger series have estimated the relative risk of depression in perimenopausal women to be in the order of twice that of premenopausal women [25].

Whilst the relative risk of depressive symptoms is increased, the actual prevalence of depressive symptoms during perimenopause is very high, being in the order of 40% in community populations [26], although the prevalence of moderate to severe symptoms is somewhat lower [27]. The rate of depressive symptoms and depressive disorders is even higher in women presenting to menopause clinics [28,29].

Whether the increase in depression seen during perimenopause in restricted to women with a past history of depressive disorders or whether perimenopause is a period of risk for new onset depression has been examined by several groups.

2.2. Women with no history of depression

In the POAS, Freeman found the risk of depressive symptoms in women with no history of depression to be increased 4 fold when perimenopausal compared with the woman's risk when she was premenopausal [8]. In the POAS and the Harvard Study of moods and cycles the risk of being diagnosed with a depressive disorder in women with no previous episodes of depression was elevated approximately two-fold [7,8]. Bromberger followed 266 women with no history of depression for seven years. The rate of major depression in this group was 15.8% [30].

2.3. Women with a past history of major depressive disorder (MDD) or bipolar affective disorder (BPD)

Women with a past history of depressive disorders are at an even greater increased risk of further depressive episodes during perimenopause. In clinical populations, women with pre-existing psychiatric conditions account for the majority of presentations. For example, of women presenting to a midlife mood clinic with

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DSM-IV major or minor depression 39% were experiencing their first ever episode, whilst 57% were suffering a relapse [31].

Five studies examining the effect of menopausal status on chronic mental illness were found. Gregory followed 47 women aged 45–55 with BPD for 17 months. 68% of the women suffered a depressive episode during perimenopause. The frequency of depressive but not manic episodes was increased compared with the woman's premenopausal years [32]. In a cross sectional study of women with bipolar disorder, MDD and schizophrenia (30 in each group), 51.6% of women reported worsened mood symptoms with menopause [33]. Payne conducted a cross sectional survey of 2412 women with MDD or BPD. Of those of perimenopausal age or greater, 26.4% reported worsening of depressive symptoms with the perimenopause [34].

The severity of vasomotor and mood symptoms in women with chronic mental illness appears greater than other perimenopausal women [35]. There is observational evidence to suggest that treatment with hormone therapy may reduce the severity of mood symptoms in perimenopausal women with BPD [36].

2.4. Symptoms of perimenopausal depression

Only two studies specifically examined the presentation of major depression in peri vs pre and postmenopausal women. Neither study found a difference in the severity of depression [37,38]. Kornstein found that perimenopausal women were more likely to have early morning waking and less likely to be irritable or suicidal [38]. However, in community populations mood swings and irritability appear to occur more commonly in peri as opposed to premenopausal women [39,40].

In our experience women often describe an 'on–off' phenomenon. That is, they experience episodes of sadness or irritability for minutes to hours which spontaneously resolve, similar to the lability which can be seen with premenstrual syndrome. It is tempting to think of new onset perimenopausal depression as a distinct entity, a menopausal equivalent of premenstrual syndrome. However, the research characterising the nature of depressive symptomatology (as opposed to major depressive disorder) in perimenopause has not been done.

Whilst there is now substantial evidence that depression is increased during perimenopause there are several possible explanations for this, including psychological, social and biological reasons. Certainly, negative life events are a very strong risk factor for the development of depression in midlife [30,41,42]. However, for the purposes of this review we have examined aspects of perimenopausal depression which might suggest an underlying biological vulnerability. For example, whether perimenopausal depression correlates with poor mood during other reproductive events or with the physical symptoms of perimenopause; and the relationship between perimenopausal depression and sex hormones.

2.5. The relationship between perimenopausal depression and depression associated with other reproductive events

Given the hormonal fluctuations associated with the perimenopause, several authors have investigated whether perimenopausal mood symptoms are more likely to occur in women who have had low mood associated with other periods of sex hormone fluctuation. Higher rates of premenstrual syndrome have consistently been found in women with perimenopausal depression presenting to specialised clinics [31,43,44] and in community dwelling women [39]. Post natal depression has been described as a predictor of perimenopausal depression in some in some but not all studies [31].

2.6. Relationship between perimenopausal depression and vasomotor symptoms

Vasomotor symptoms (VMS) are a prominent feature of perimenopause, and correlate with changing hormone levels [45]. The 'domino theory' is one potential explanation for the increase in depression at perimenopause. The 'domino theory' hypothesises that increased depression in perimenopausal women is related to distress from vasomotor symptoms such as disturbed sleep from night sweats.

Studies of women presenting to menopause clinics and community surveys have found a 2–4 fold risk of depressive symptoms in women with VMS [27,28,46]. However, in women with no previous history of depression Bromberger found no association between VMS and first onset depression [30]. In contrast, Cohen found self reported VMS to increase the risk of first onset depression [7]. Evidence is also conflicting as to whether VMS are associated with more severe depression [37,44].

In clinical trials, the antidepressant effect of estradiol appears to be independent of any improvement in vasomotor symptoms [47,48]. Overall, the relationship between VMS and perimenopausal depression remains unclear.

2.7. Sex hormones and perimenopausal depression

The evidence to date supports the notion that women with perimenopausal depression do not suffer from a hormonal abnormality as such, but have an abnormal response in the brain to the normal hormonal fluctuations associated with the menopausal transition [49]. Interestingly though, one study has shown that SNPs associated with 6 genes involved in the production and metabolism of oestrogen are associated with an up to 12 fold increase in the risk of depressive symptoms in perimenopause [50].

During perimenopause, there are significant fluctuations in serum FSH and estradiol levels. In women who develop depression during perimenopause, the depression appears to correlate with these hormonal fluctuations in some studies. This contrasts to women who do not develop depression, who experience the same hormonal fluctuations yet remain euthymic. For example, in a 6 week longitudinal study of women presenting to a menopause clinic [51], CES-D and hormone profiles were measured six weeks apart. Those women whose FSH decreased by 50% over 6 weeks had a significant improvement in mood. Likewise, those women whose CES-D score improved by 50% had a significant decrease in FSH. This suggests that an improvement in ovarian function was associated with improved mood. In the Penn Ovarian Ageing study mean FSH levels were inversely related to mood swings and irritability, and within woman fluctuations of FSH and estradiol were associated with worsened mood [39].

The differing neural response to oestrogen in some women is also supported by a small clinical trial of oestrogen therapy in perimenopausal women with treatment resistant depression. Women whose mood improved with oestrogen had reductions in right frontal quantitative EEG readings as compared to non-responders [52]. Yet, there was no correlation between mood and absolute serum estradiol levels.

The relationship between sex hormones and mood in women remains poorly understood. Overall, studies suggest that in some but not most women, changes in levels of FSH and estradiol during the perimenopause, negatively influence mood.

Further information regarding the effects of oestrogens in the brain and on mood can be found in several thorough reviews [53–55]. The current knowledge of oestrogen action in the brain these reviews detail is supportive of an antidepressant effect of oestrogens, however most of the data is derived from animal studies.

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Table 1
Clinical trials of pharmacotherapy in perimenopausal women.

Author	Diagnoses (no.)	Intervention (no. women)	Remission rate	Comments
Soares (2001)	MDD (26), dysthymia (11) minor depression (13) Mean baseline MADRS: E2 24.6; placebo 21.84	RCT 100 mcg transdermal E2 or placebo for 12 weeks, followed by 4 week washout	E2 68%, placebo 20%	54% first onset depression Effect on mood sustained at 4 weeks, despite return of VMS
Schmidt (2000)	MDD (7) minor D (27) Mean HAMD: E2 16.6; placebo 16.4	3 week RCT 0.05 mcg E2 (16) vs placebo (18), then all patients on E2 for 3 weeks followed by 1 week E2/MPA		Full or partial response in 80% E2 vs 22% placebo. VMS or duration of estradiol treatment did not influence outcome
Rasgon (2002)	MDD (16)	8 week open trial 10 treatment naïve women given ET alone 6 nonpartial responders to fluoxetine given adjunctive ET	ET only: 6/10 ET/F: 3/6	
Cohen (2003)	Peri (10) Post (12)	4 week open label Rx w 100 mcg transdermal E2	Peri: 6 women Post: 2 women	Response not associated with change in VMS
Shanklat (2005)	Peri (20) Post (22)	Open trial 1.25 mg oral oestrogen for 4 weeks	5/40 who completed	MADRS 20–11.5
Morgan (2006)	Mean baseline MADRS 20 MDD on SSRI (17) (partial responders)	6 weeks 0.625 mg CEE (11) vs placebo (6)		Significant reduction in HAM-D w CEE c/w placebo
Joffe (2011)	72 peri and postmenopausal women with unipolar depressive disorders, hot flashes and insomnia (≥ 3 awakenings/night) MADRS baseline 20.9	8 week RCT transdermal E2 0.05 mg/d (27) zolpidem 10 mg/d (31)		Mean MADRS decreased 20.9–11.8; NS difference between groups Increased E2 levels associated with improved mood in peri but not post women, regardless of treatment group. Improved VMS did not predict improvement in mood
Iglesias (2010)	MDD peri (13) post (23)	24 week open label trial venlafaxine XR – variable dosing		HAM-D (22 → 7). NS difference between peri and post
Lasser (2005)	DSM-IV depressive disorder (16)	Open label 8 week trial of venlafaxine	75%	Adverse events: peri 30% post 0%
Soares (2010)	MDD (40)	8 week open trial of 150–300 mg quetiapine	15/40	SEs common (62% GI sx)
Komstein (2010)	387 peri and post	8 week flexible dose RCT desvenlafaxine 100–300 mg vs placebo	Des: 38.2% P: 22%	17 pts >50% reduction in MADRS Response 58.6% vs 31.6%
Freeman (2006)	Depression (20)	8 week open label trial escitalopram		
Soares (2003)	33 peri and post	12 weeks citalopram alone (22) vs 8 weeks citalopram + E2 (13) (enrolled in adjunctive arm if failed to achieve remission after 4/52 E2 alone)	Cit (13) Cit/E2 (11)	Improvement in all domains
Joffe (2001)	MDD (22) on stable dose ERT MDD	Open trial mirtrazepine 30–45 mg/d	14/16	
Soares (2006)	Depressive disorders (40)	Open trial escit 10–20 mg or E2 5 mcg/d + PI mg	Escit 75% EP 25%	
Cassano (2005)	Outpatients MDD pre (121), peri (28), post (35)	8/52 open study fluoxetine 20 mg/d	15/28 (54%)	NS difference between groups

MDD, major depressive disorder; Minord, minor depression; Pre, premenopausal; Peri, perimenopausal; Post, postmenopausal; NS, non significant; MADRS, montgomery asberg depression rating scale; HAMD, Hamilton Mood Scale – Depression; E2, estradiol.

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In animal studies oestrogen receptors (ERs) to many parts of the brain with ER alpha being found particularly in the hypothalamus, hypothalamic preoptic area and amygdala and ER beta being more wide spread, in the pituitary, hippocampus, cerebral cortex, midbrain and brainstem [55]. Estradiol is involved in regulating activity of the neurotransmitters serotonin and acetylcholine both of which are key to the pathogenesis of depression [56]. In animals studies estradiol modulates the synthesis of serotonin [57], serotonin reuptake [58], serotonin receptor transcription [59] and the response to serotonin stimulation [60]. In rats, estradiol has been shown to have many interactions with noradrenaline, a neurotransmitter involved in the modulation of drive, energy, sleep regulation, learning and arousal [54]. Estradiol regulates noradrenergic (NA) activity by increasing NA release, decreasing NA reuptake and decreasing the number and sensitivity of dopamine D2 receptors [61].

The fluctuations and eventual reduction in estradiol levels that characterise the perimenopause may directly cause all of the observed physical and psychological symptoms through altered activation of key brain regions and structures that control each of these symptoms [62,63].

2.8. Hormonal and antidepressant therapies for perimenopausal depression

Whilst there may be much animal data to suggest that estradiol has an antidepressant effect the efficacy of hormone therapy as a treatment for perimenopausal depression has not been examined in large randomised controlled trials. However, sixteen studies have trialled pharmacological therapy specifically for perimenopausal depression (Table 1). Nine of these studies include oestrogen therapy alone or as an adjunct. Overall, oestrogen therapy appeared effective in improving depressive symptoms. However, these studies involve small numbers of women with variable degrees of depression, treated for short durations, and are often unblinded and underpowered.

To date the largest trial of oestrogen therapy in perimenopausal depression was conducted by Soares [64]. This 12 week placebo controlled study in 50 perimenopausal women with varying degrees of depression showed remission of depression in 68% of women treated with 100 mcg transdermal estradiol vs a 20% remission rate in the placebo group. The antidepressant effect was apparent even after a 4 week washout period, despite the recurrence of vasomotor symptoms. In another placebo controlled trial of 34 women with perimenopausal depression, estradiol therapy for 3–6 weeks, resulted in symptom improvement in 80% of women, vs only 22% in the placebo group [47]. A placebo controlled trial of 16 women with major depressive disorder found beneficial effects of adjunctive conjugated equine oestrogen in women who had only a partial response to SSRIs [65]. The SSRI citalopram and the SNRI's duloxetine and venlafaxine have been shown to improve both mood and vasomotor symptoms [66,67].

3. Discussion

The temporal association of lowered mood and perimenopause suggests that in some women, the normal changes in reproductive hormones associated with the menopause increases the risk of depressive symptoms or an episode of major depression. That perimenopausal women do not suffer from more negative life events than pre or post menopausal women adds further weight to the plausibility of an endocrine contribution to perimenopausal depression [68].

Whilst oestrogen therapy appears effective in small trials one of the difficulties of using oestrogen therapy longterm in clinical practice is the need for women with an intact uterus to be given a progestin to prevent endometrial hyperplasia. Progestins can, however, worsen depression, or negate the positive effects of estradiol, in approximately 30% of women [69]. This could potentially explain the poor remission rate in the hormone therapy treated group in a randomised comparison with escitalopram [70].

A useful alternative to combined hormone therapy is tibolone, a synthetic steroid with oestrogenic, androgenic and progestogenic effects [71]. Tibolone also increases b-endorphin levels [72] and reduces sex-hormone binding globulin, thereby increasing serum free testosterone concentrations [73]. While these properties could theoretically induce an antidepressant response, tibolone has not been trialled for perimenopausal depression.

Selective oestrogen receptor modulators (SERMs) such as raloxifene are another potential alternative to oestrogen therapy. SERMs have mixed agonist and antagonist effects on the oestrogen receptors at different sites [74]. SERMs have not been trialled in perimenopausal depression, though there is preliminary evidence of benefit in severe mental illness [75].

Given the suggestive animal and human trials, hormone therapy may be a viable alternative in some women. However, rigorous, well designed, adequately powered randomised controlled trials are required in order to change routine practice. Further research needs to assess hormonal agents which can be safely given for long periods of time, as required in clinical practice.

With adequate research, hormone therapy may be an alternative or an adjunct to conventional antidepressants for the treatment of perimenopausal depression. Adjunctive therapies may improve symptoms in women with refractory depression. Standalone hormonal therapy has the benefit of decreasing fracture risk, a major cause of morbidity and mortality in older women. Being able to confidently treat a woman's vasomotor symptoms and depression with a single agent would also be useful clinically to maximise outcomes and minimise side effects.

4. Conclusion

Traditional and novel forms of hormonal therapy, including tibolone and SERMs should be further investigated for the treatment of depression in perimenopausal women. This is worth investigating to provide women with a viable treatment option for those not wanting, not, requiring or not responsive to current antidepressant medications. The sheer numbers of women suffering with perimenopausal depression combined with the limitations of current therapies make the search for better treatments a clinical priority.

Contributors

Roisin Worsley wrote the manuscript and did the literature search; Susan R. Davis and Jayashri Kulkarni provided guidance and assistance in the writing and editing of the manuscript; Henry Burger proofread the manuscript and gave sagely advice; Emorfia Gavrilidis, Zoe Gibbs and Stuart Lee assisted with the literature review. All the authors have seen and approved the final version of the draft.

Competing interest

Henry Burger has been associated with Pfizer, and all the remaining authors had no potential conflict of the interest.

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Appendix B: The Alfred Ethics Committee Certificate of Approval

CC: Stuart Lee

TheAlfred

ETHICS COMMITTEE CERTIFICATE OF APPROVAL

This is to certify that

Project No: 311/09

Project Title: Characterizing the symptom presentation of perimenopausal depression and a pilot of tibolone as a hormonal treatment for depression in perimenopause

Principal Researcher: Professor Jayashri Kulkarni

Protocol No: 311/09

Participant Information and Consent Form version 2 **dated:** 2-Nov-2009

was considered by the Ethics Committee on ***22-Oct-2009*** *and* ***APPROVED*** *on* **16-Nov-2009**

It is the Principal Researcher's responsibility to ensure that all researchers associated with this project are aware of the conditions of approval and which documents have been approved.

The Principal Researcher is required to notify the Secretary of the Ethics Committee, via amendment or progress report, of

- Any significant change to the project and the reason for that change, including an indication of ethical implications (if any);
- Serious adverse effects on participants and the action taken to address those effects;
- Any other unforeseen events or unexpected developments that merit notification;
- The inability of the Principal Researcher to continue in that role, or any other change in research personnel involved in the project;
- Any expiry of the insurance coverage provided with respect to sponsored clinical trials and proof of re-insurance;
- A delay of more than 12 months in the commencement of the project; and,
- Termination or closure of the project.

Additionally, the Principal Researcher is required to submit

- A Progress Report on the anniversary of approval and on completion of the project *(forms to be provided)*;

The Ethics Committee may conduct an audit at any time.

All research subject to the Alfred Hospital Ethics Committee review must be conducted in accordance with the National Statement on Ethical Conduct in Human Research (2007).

The Alfred Hospital Ethics Committee is a properly constituted Human Research Ethics Committee in accordance with the National Statement on Ethical Conduct in Human Research (2007).

SPECIAL CONDITIONS

None

SIGNED: [redacted]
Chair, Ethics Committee (or delegate)

R. FREW
SECRETARY
ETHICS COMMITTEE

Please quote Project No and Title in all correspondence

Appendix C: Monash University Human Research Ethics Committee Approval

MONASH University

Monash University Human Research Ethics Committee (MUHREC)
Research Office

Human Ethics Certificate of Approval

Date:	**26 May 2010**
Project Number:	**CF10/1342 - 2010000721**
Project Title:	**Characterizing the symptom presentation of perimenopausal depression and a pilot of tibolone as a hormonal treatment for depression in perimenopause**
Chief Investigator:	**Prof Jayashri Kulkarni**
Approved:	**From: 26 May 2010 to 26 May 2015**

Terms of approval

1. The Chief investigator is responsible for ensuring that permission letters are obtained, if relevant, and a copy forwarded to MUHREC before any data collection can occur at the specified organisation. **Failure to provide permission letters to MUHREC before data collection commences is in breach of the National Statement on Ethical Conduct in Human Research and the Australian Code for the Responsible Conduct of Research.**
2. Approval is only valid whilst you hold a position at Monash University.
3. It is the responsibility of the Chief Investigator to ensure that all investigators are aware of the terms of approval and to ensure the project is conducted as approved by MUHREC.
4. You should notify MUHREC immediately of any serious or unexpected adverse effects on participants or unforeseen events affecting the ethical acceptability of the project.
5. The Explanatory Statement must be on Monash University letterhead and the Monash University complaints clause must contain your project number.
6. **Amendments to the approved project (including changes in personnel):** Requires the submission of a Request for Amendment form to MUHREC and must not begin without written approval from MUHREC. Substantial variations may require a new application.
7. **Future correspondence:** Please quote the project number and project title above in any further correspondence.
8. **Annual reports:** Continued approval of this project is dependent on the submission of an Annual Report. This is determined by the date of your letter of approval.
9. **Final report:** A Final Report should be provided at the conclusion of the project. MUHREC should be notified if the project is discontinued before the expected date of completion.
10. **Monitoring:** Projects may be subject to an audit or any other form of monitoring by MUHREC at any time.
11. **Retention and storage of data:** The Chief Investigator is responsible for the storage and retention of original data pertaining to a project for a minimum period of five years.

[redacted]

Professor Ben Canny
Chair, MUHREC

Cc: Dr Stuart Lee; Zoe Gibbs

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