Published in final edited form as:

Menopause. 2010 July ; 17(4): 815–822. doi:10.1097/gme.0b013e3181d763d2.

Summary of the NIA-sponsored Conference on Depressive Symptoms and Cognitive Complaints in the Menopausal Transition

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Summary

This NIA-sponsored workshop was aimed at understanding the impact of the menopausal transition on mood symptoms and cognitive disorders during the menopausal transition and identifying research priorities for further investigation. Longitudinal studies provide insights into the frequency of these problems in representative samples of midlife women. The majority of women do not experience serious depressive symptoms during the transition, but a subgroup of women is at increased risk. Slight changes in memory function and processing speed are evident during the transition, and physiological factors associated with hot flashes may contribute to memory problems. Clinical trial evidence indicates that estradiol therapy can be effective in treating perimenopausal depression. There is some limited evidence of a cognitive benefit with estrogen alone therapy in younger

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Conflicts of interest/Disclosures: Dr. Maki has received consultant/advisory board services to the Council on Menopause Management and research support from Wyeth Pharmaceuticals. Dr. Freeman has disclosed grants/research support from Forest. Dr. Henderson has disclosed consultant/advisory board services to Alexander Foundation for Women's Health, Council on Menopause Management, Geriatric Neurology Section of the American Academy of Neurology; John Douglas French Alzheimer's Foundation, and the National Aphasia Association. Dr. Newhouse has disclosed consultant/advisory board services to Neuroderm; grants/research support from NIA, NIMH, NIAMS, Lilly, Novartis; and speaker's bureau services to Pfizer. Dr. Soares has disclosed grants/research support from Allergan National Centre of Excellence, AstraZeneca, Canadian Institute of Health Research, Lilly, Hamilton Community Foundation, Lundbeck, Physicians Services Incorporated Foundation, Wyeth; and research support, consultant/speaker's bureau/advisory board services to AstraZeneca, Bayer Healthcare Pharmaceuticals, and Wyeth. Drs. Schmidt, Greendale, Shively, and Scott have nothing to declare.

postmenopausal women, and stronger evidence that certain forms of combination hormone therapy produce modest deficits in verbal memory in younger and older women. Identifying a cognitively neutral or beneficial combination therapy for the treatment of menopausal symptoms in naturally menopausal women is an important goal for future research. Pharmacological challenge studies bridge the basic science and clinical literatures to provide insights into the extent to which changes in endogenous and exogenous hormones and other neurotransmitter systems contribute to cognitive and mood problems. Routine evaluation of depressive symptoms in perimenopausal women is warranted by the literature. Quick and valid screening tools for assessing depression in the clinic are available on-line and free of charge.

Keywords

Menopause; Cognition; Mood; Perimenopause; Depression

The NIH-Sponsored Pre-Symposium entitled, “Depressive Symptoms and Cognitive Complaints in the Menopausal Transition” was held on September 29, 2009 at the Manchester Grand Hyatt in San Diego, California. This Pre-Symposium was held in conjunction with, and on the day before the Annual Meeting of the North American Menopause Society (NAMS). The Pre-Symposium was supported by Award Number R13AG033944 from the National Institute on Aging and also received support from the Office of Research on Women's Health (ORWH) and NAMS.

The Pre-Symposium brought together leading scientific experts, menopausal healthcare providers, and researchers in an interactive forum with the following goals: imparting state-of-the-science knowledge about the impact of the menopause on cognition and mood; understanding the clinical relevance of recent findings; identifying scientific gaps, and reviewing the diagnosis and treatment of cognitive and mood disorders in peri- and postmenopausal women. The Pre-Symposium was divided into a morning session focusing on depressive symptoms in the menopausal transition, and an afternoon session on cognitive function in the menopausal transition. There were four speakers per session, and each session was structured to cover four methodological approaches including longitudinal cohort studies, randomized intervention trials, pharmacological challenge studies, and clinical diagnosis. Interactive panel discussions focused on translating research findings to clinical practice. Relevant questions included who is at risk for depressive symptoms and cognitive decline, to what extent are endocrine markers effective in identifying at-risk individuals or guiding treatment decisions, and how should clinicians approach diagnosis. Below we summarize the proceedings of the workshop for each topic.

Part I. Mood and the Menopausal Transition

Risk of Depression During the Menopausal Transition

Women and clinicians generally identify the approach of menopause by changes in menstrual bleeding. Hot flashes, which are widely considered to be the cardinal symptom of menopause, also signify the menopausal transition for many women. Depressive symptoms, poor sleep, aches and joint pains are other frequent complaints in this transition period, but whether these symptoms are associated with hormone changes of the menopausal transition is controversial.

Identifying the risk of depression in the menopausal transition is particularly important because of its significant disability and its strong associations with other diseases in mid-life women such as metabolic syndrome, osteoporosis, and cardiovascular disease.¹⁻³ Although some epidemiologic studies found no significant association between depression and menopausal

status, several recent longitudinal studies identified an increased risk of depressed mood in the transition to menopause.⁴⁻⁹

Three large prospective cohort studies indicate that the likelihood of depressed mood is approximately 30% to three times greater in the menopausal transition compared to the premenopausal stage.⁶⁻⁸ Women with a history of depression are nearly five times more likely to have a diagnosis of major depression in the menopausal transition.⁵ Most importantly, women with no history of major depression are two to four times more likely to report depressed mood in the menopausal transition compared to the premenopausal stage.^{6, 7} The changing hormonal milieu contributes to depression in the transition period as evidenced by the associations of depressed mood with menopausal stage, variability in estradiol, and increasing FSH levels.^{5, 6, 10} Other risk factors for depression in these longitudinal studies include poor sleep, hot flashes, stressful or negative life events, lack of employment, age and race.

These observations of an increased risk of depression in perimenopausal women support the concept that the perimenopausal stage, which is framed by the changing hormonal milieu of ovarian aging, is a “window of vulnerability” for some women.

Clinical Trials of Estrogen and Depressive Symptoms

Estrogen alters monoaminergic systems (e.g., serotonin, noradrenalin) that are intimately involved in mood and behavior regulation. For example, estrogen increases serotonin receptor density in select brain regions such as hypothalamus, preoptic area and amygdala. Estrogen also increases noradrenalin availability and synthesis, while reducing its turnover.

Findings from a double-blind, placebo-controlled, randomized trial demonstrated that 17 β -estradiol 100 μ g given transdermally for 12 weeks is efficacious in the treatment of depression in perimenopausal women, with remission rates as high as 60-80%¹¹. Conversely, transdermal estradiol has failed to show antidepressant properties when given to postmenopausal women in at least one randomized trial¹². Together, these studies suggest that the menopause transition may constitute not only a “window of vulnerability” for the occurrence of depression in some women but also a “window of opportunity” for the use of estrogen-based strategies for the management of depression.

Role of Gonadal Steroids in Perimenopause-Related Depression: Evidence from Pharmacological Challenge Studies

Schmidt and his colleagues have examined the effects of estrogen withdrawal and the recent onset of hypogonadism on mood symptoms using two strategies. First, Harsh et al.¹³ administered a gonadotropin hormone releasing hormone (GnRH) agonist for two to three months to 53 regular cycling, premenopausal women. In contrast to previous reports from gynecology clinic-based samples^{14, 15}, all women had the absence of current or past psychiatric illness confirmed by a structured psychiatric diagnostic interview and completed daily symptom ratings for two months prior to the study entry to confirm the absence of significant mood or behavioral symptoms associated with their menstrual cycle. Additionally, all women had normal gynecologic and medical exams. Mood and behavioral symptoms during GnRH-agonist were measured by the Beck Depression Inventory (BDI) and a self-report symptom rating form completed on a daily basis. Plasma hormone measures confirmed that the GnRH agonist suppressed the secretion of both ovarian steroids and gonadotropins. Only three women (5.7% of the sample) reported BDI scores greater than seven (suggestive of clinically significant symptoms of depression) and in only one of these women did the elevated BDI scores persist beyond two weeks duration. In contrast to the relative absence of depressive symptoms in these women, we did observe the significant appearance of several symptoms including both daytime and nocturnal hot flashes, disturbed sleep and diminished libido. Thus,

in otherwise healthy women the induction of neither hypogonadism nor hot flushes (with an accompanying sleep disturbance) uniformly precipitated depressive symptoms.

In a second ongoing study, we are evaluating the effects of the acute withdrawal of estradiol therapy in women with and those without a past history of perimenopausal depression. Preliminary results suggest that estradiol withdrawal induces depressive symptoms in women with a past history of perimenopausal depression, but not in those without such a history. No significant depressive symptoms emerged in the women lacking a history of a past perimenopausal depression who were either withdrawn or maintained on estradiol therapy. Thus, in contrast to our findings with GnRH agonist-induced hypogonadism in premenopausal women with no past psychiatric history, estradiol withdrawal in women with a past history of perimenopausal depression triggers mood symptoms. These data are consistent with findings from epidemiologic studies showing that, for a subgroup of women, the endocrine events of the late menopause transition may represent important triggers for mood destabilization and the onset of depression. Both the markers of this risk and the mechanisms underlying estradiol withdrawal-induced depressive symptoms remain to be identified.

In summary, endocrine studies of depression during the menopause transition suggest the following:

1. Depression during the menopause transition is not associated with a simple deficiency or excess of reproductive hormones, as is the case in other reproductive endocrine-related mood disorders;
2. Pharmacologic induction of hypogonadism and estradiol withdrawal is not uniformly associated with depressive symptoms, but in some women estradiol withdrawal appears to be an important physiologic trigger for the onset of mood disturbance.
3. Similarly, based on the antidepressant efficacy of estradiol therapy, declining estradiol secretion may play a role in the pathophysiology of depression during the menopause transition (in contrast to depressions in the postmenopause).

Recognizing Perimenopausal Depression

Depression is a common and disabling illness. The gender difference in depression rates is most pronounced during the reproductive years, and at times women may have twice the rates of depression as men¹⁶. Sadness, the hallmark symptom of depression, is a normal emotion and common during times of change. Treatment of depression is warranted when it is persistent, causes functional impairment, or is accompanied by other physical and cognitive symptoms. Even “minor” depression – states that do not meet diagnostic criteria for a major depressive episode – can cause significant impairment. It may be challenging to distinguish between the physical symptoms of menopause and those of depression. Nevertheless, when mindful of DSM-IV criteria and available screening tools, it is possible to improve the detection of depression.

DSM-IV criteria for depression include the presence of five or more symptoms during the same 2-week period of the symptoms listed below.¹⁷ At least one of these symptoms must include depressed mood or loss of interest or pleasure in most activities.

1. Depressed mood
2. Loss of interest or pleasure in most activities
3. Significant weight loss/gain or increased/decreased appetite
4. Insomnia or hypersomnia
5. Psychomotor agitation or retardation

6. Fatigue or loss of energy
7. Feelings of worthlessness or excessive guilt
8. Diminished concentration or indecisiveness
9. Recurrent thoughts of death (not just fear of dying) or suicidal ideation

One challenge in primary care is the low detection rate in diagnosing depression, with the best detection rates estimated to be 36-56%.¹⁸ Patient and clinician factors also play a role. Patients infrequently report stressors and frequently report somatic symptoms. Appointment times are short, making a lengthy assessment of depression challenging. One screening instrument that is particularly helpful in quickly screening for depression is the Patient Health Questionnaire (PHQ-9).^{19, 20} The PHQ-9 is a 9-item, self-report questionnaire that is useful in clinical settings because it is easy to score and items are linked to DSM-IV depression criteria. The questionnaire can be used to assess and track treatment response.²¹ Both English and Spanish versions are available free of charge on line.

A final note, when screening for perimenopausal depression, clinicians should consider key additional risk factors include previous episodes of depression, psychosocial stressors, and severe climacteric symptoms (e.g., sleep disturbance, vasomotor symptoms).^{5, 22}

Depression as a Risk Factor for Cardiovascular Disease

Depressive disorders and coronary heart disease (CHD) are leading causes of the global burden of disease. Both diseases are inversely related to socioeconomic status. Depression and CHD are comorbid; although the nature of the relationship between these two diseases is unclear, when depression is present CHD prognosis is poor. CHD is the leading cause of death of women. Depression is twice as likely in women as men. Thus, the comorbidity of CHD and depression may be especially important for women's health. In women depression is associated with life phases that are characterized by changes in reproductive system function including puberty, the late luteal phase of the menstrual cycle, the postpartum period, and the perimenopause. Nonetheless, the majority of animal models of depression are male.

We have developed an adult female nonhuman primate model of depression in cynomolgus monkeys, which have been used effectively for decades to model CHD risk in women²³. Like women, female cynomolgus monkeys develop atherosclerosis in their coronary arteries. Coronary artery atherosclerosis and its sequelae cause CHD. Like women, socially stressed monkeys are more likely to become depressed. Also like depressed women, depressed monkeys are insensitive to negative feedback in dexamethasone suppression tests and have smaller anterior hippocampi and lower neural serotonin 1a receptor binding throughout brain areas associated with depression. Depressed monkeys also have higher heart rates, dyslipidemia, poor ovarian cyclicity characterized by lower ovarian steroid concentrations, and lower levels of physical activity than their nondepressed counterparts; all of these are risk factors for coronary artery atherosclerosis and CHD. Depressed monkeys develop more than four times the coronary artery atherosclerosis as their nondepressed counterparts.

Female cynomolgus monkeys are a unique model in which to study the comorbidity of depression and CHD. Using this model we are addressing the question of whether depression causes coronary artery atherosclerosis.

Summary Depressive Symptoms and the Menopausal Transition

Ovarian steroids regulate many of the signaling pathways, neurocircuits and behaviors that are hypothesized to be abnormal in depression. Recent evidence from prospective studies suggests that for a subgroup of women the endocrine events during the menopause transition play a role

in the onset of depression. Additionally, although perimenopausal depression is not caused by abnormalities of basal ovarian hormone secretion, this disorder, nonetheless, may be effectively treated with estradiol. The specificity of the relationship between the endocrine events of the menopause transition and depression in these women is further suggested by reports of the lack of antidepressant action of estradiol therapy in postmenopausal depressed women. Nonetheless, studies in which menopause is induced pharmacologically demonstrate that estradiol withdrawal and hypogonadism are sufficient to trigger depression in only a subgroup of women. Non-human primate studies are exploring depressive symptoms as a risk factor for the development of cardiovascular disease. Future studies need to identify the biochemical factors and markers of risk underlying the differences between those women who remain asymptomatic during the menopause transition and those who develop depression. The biological underpinning of this differential behavioral phenotype also may serve to reconcile and/or predict differences in response to hormone therapy.

Part II. Cognition and the Menopausal Transition

Cognitive Change During the Menopausal Transition

A majority of women report memory problems during the menopause transition, but studies of measured cognitive performance during the menopausal transition are rare.²⁴ The first study to examine the relationship between menopausal stage and memory was a cross-sectional investigation of women enrolled in the Melbourne Women's Midlife Health Project²⁵. Women in the early perimenopause, late perimenopause, and postmenopausal stages did not differ in terms of their memory performance. In a secondary analysis, women who initiated hormone therapy before the final menstrual period had higher memory scores compared with women who initiated after menopause.

The relation between reproductive stage and measured cognitive performance has been the subject of only three published longitudinal studies.²⁶⁻²⁸ These longitudinal studies included estimates of memory performance during the premenopausal stage. A cohort study involved 573 Chinese women aged ~46 yrs at baseline and an average education of ~6.5 years.²⁶ Comparison of cognitive performance among those who remained pre-menopausal to those who became perimenopausal during a follow up interval of 18 months showed that, as expected in this age range, performance on all tests improved. However, those who transitioned to perimenopause had statistically significantly less improvement on a test of verbal **fluency** than those who remained premenopausal. The Chicago site of the Study of Women's Health Across the Nation (SWAN) initiated a site-specific study of measured cognitive performance (verbal and working memory) at SWAN baseline (the other six SWAN sites did not assess cognition at the outset of SWAN).²⁷ After two years of follow-up in ~800 women aged 42-52 at baseline, adjusted for socio-demographics there were small time-related improvements in both cognitive domains, but no significant effects related to menopausal stage were identified.²⁷

In contrast to the two-year results from Chicago-SWAN, a four-year longitudinal analysis based on data from the full SWAN cohort found effects of the menopausal transition and of hormone use on measured cognitive performance (SWAN added tests of cognitive processing speed, verbal episodic memory and working memory to annual examination at follow-up visit four).²⁸ Processing speed improved with repeated testing during pre-, early peri- and postmenopause, but not during late perimenopause. Similarly, verbal memory scores improved with repeated testing for premenopausal and postmenopausal participants, but not for perimenopausal participants. Former hormone use (used prior to the final menses) was associated with better processing speed and verbal memory. In contrast, current hormone during postmenopause predicted poorer processing speed and verbal memory, compared to performance during premenopause. These newer SWAN results likely differ from those of the Chicago site-specific report because the SWAN cohort sample size was three times as large,

follow-up was twice as long, and the effects of prior and current hormone use were accounted for. All other published investigations of MT stage and cognition have been cross sectional.²⁹

Clinical Trials of Estrogen and Cognition

The primary outcome of interest in clinical trials of estrogen and cognition is commonly a test of verbal memory, typically a word-list learning task or a paragraph recall task that include measures of both immediate recall and delayed recall. A focus on verbal memory is justified by its relevance to dementia risk. Deficits in verbal memory have been shown to be the earliest neuropsychological predictor of conversion to Alzheimer's disease in a number of studies. Additionally, females on average outperform males on these tasks, women complain about lapses in memory for names and other verbal information during the perimenopause, and new evidence from SWAN reviewed above demonstrates that women show performance deficits on verbal tests during the perimenopausal stage.²⁸

Given certain patterns in findings across clinical trials, it is helpful to distinguish the effects of estrogen alone versus estrogen plus progesterone and the effects in younger (i.e., less than 65 years) versus older (i.e., greater than 65 years) postmenopausal women.³⁰ Trials of estrogen alone in younger postmenopausal women generally have included small sample sizes (i.e., less than 100) but show some benefit to verbal memory. A recent study of transdermal estradiol revealed benefits on a test of verbal memory, but the benefit was evident on outcome measures relating to error monitoring and other executive functions.³¹ Trials of estrogen alone in older women consistently show neutral effects on verbal memory. Studies of estrogen plus progesterone treatment in younger postmenopausal women reveal a reliable, but small deficit in verbal memory when the treatment is conjugated equine estrogen plus medroxyprogesterone acetate (CEE/MPA). Only one trial in younger postmenopausal women used a different estrogen plus progesterone intervention, and that trial revealed a beneficial effect of estradiol valerate and dinogest.³² Studies of estrogen plus progesterone in older women parallel those in younger women and demonstrate a modest deficit in verbal memory with CEE/MPA. Cyclic oral estradiol and norethindrone acetate had neutral effects on verbal memory in older women, though a subanalysis revealed that treatment improved verbal memory in women whose baseline verbal memory was above average.³³ The finding that the baseline health or cognitive status of women modulates the effects of estrogen on cognition has been reported in other studies, including the Women's Health Initiative Memory Study (WHIMS) and the Women's Estrogen for Stroke Trial (WEST).^{34, 35}

What other factors might modulate the impact of hormone therapy on cognition? There is more evidence of overall benefit in younger versus older women, but CEE/MPA produces modest decrements in verbal memory in both age cohorts. There have been several demonstrations of neutral cognitive effects of other HT formulations in older women, including estradiol. In these studies it is difficult to determine whether the critical factor associated with benefit is young age and/or other factors confounded with young age including less time since the final menstrual period or better health. Three studies in older women suggest that the greatest cognitive benefits are evident in women with intact cognitive function. There is preliminary evidence of a negative correlation between memory function and hot flashes, but this relationship is evident only when hot flashes are measured with ambulatory monitors. Future studies are needed to better understand the phenotype of women who might show cognitive benefit with hormone therapy.

Role of Gonadal Steroids in Perimenopause-Related Cognitive Changes: Evidence from Pharmacological Challenge Studies

The loss of estradiol production in postmenopausal women has profound negative effects on a number of organ systems including the brain. As reviewed above, loss of estrogen support

during the peri- or early postmenopausal period in women can produce measurable and significant impairment of performance on certain cognitive tasks and estradiol administration appears to prevent these changes and improve cognitive performance in some models.

In an attempt to understand how estrogen effects on brain function are mediated, we have been focusing on the activities of brain central cholinergic system. Several decades of research support the critical role of brain cholinergic systems in cognition in humans, particularly in learning, memory formation, and attention. As the cholinergic system is a neurotransmitter system that projects to all regions of the brain and has been shown to decline in aging, it remains the best candidate neurotransmitter system to be related to cognitive changes in aging. The cholinergic changes that occur with aging may be one explanation for the common pattern of alterations in cognitive performance and brain activation seen in older adults on tests of attention, working memory and episodic memory. The cholinergic hypothesis is general enough to provide an underlying neurobiological framework for these age-related changes. For example, decreases in cholinergic functioning may slow cognitive processing for older adults and result in less efficient cognitive processing.

Estradiol has significant positive effects on brain cholinergic neurons, interacts with trophic factors on neuronal development and plasticity, and improves cholinergic-related cognitive processes in animal models. We have extended the studies to human models to investigate whether estradiol effects on human cognitive functioning are mediated at least in part through cholinergic system activity.

Our studies show that estradiol appears to improve cholinergic function as measured by increased resistance to anti-cholinergic blockade in normal postmenopausal women.^{36, 37} This improvement may be dose and domain specific, i.e. lower doses improves primarily attentional functioning, higher doses may influence episodic memory. Effects of estradiol on cholinergic function related to episodic memory may be age-specific, with younger women showing benefit but older women showing no benefit or impairment. This result provides direct experimental support for the “critical period hypothesis”. Addition of progesterone to estradiol appears to partially or completely counteract the ability of estrogen to enhance its attention and speed after cholinergic blockade. Intriguingly, the selective estrogen receptor modulator tamoxifen appears to decrease attentional and long-term recall impairment produced by cholinergic antagonists and improves spatial working memory performance. APOE genotype, a known risk factor for Alzheimer's disease and cholinergic dysfunction appears to modulate the directionality and magnitude of the effect of positive estrogen-like effects of tamoxifen on cognition following cholinergic blockade. Taken together, these results provide strong support for our original hypothesis that the ability of estradiol and related compounds to modify cognitive functioning in old age and/or partially prevent cognitive deterioration or neurodegenerative disorders may be related to effects on the brain cholinergic system.

Recognizing Cognitive Disorders

In recognizing cognitive disorders, it is useful to distinguish among dementia, mild cognitive impairment (MCI), and cognitive aging. Dementia entails substantial functional decline, and Alzheimer's disease and other late-life dementias are an ever-increasing burden in an aging population. This is a burden that affects women disproportionately. Dementia is preceded by a transitional stage of cognitive decline, and the term MCI is increasingly applied to patients meeting research criteria believed to characterize incipient dementia. The inference is that such patients already have pathological changes associated with dementia, but the pathological burden is still modest in extent or has not yet overwhelmed innate compensatory mechanisms. The concept of cognitive aging is closely related to that of MCI. Cognitive skills vary with age. For many aspects of cognition — but not all — cognitive aging represents detrimental change, beginning in middle age and accelerating in old age. The underlying assumption,

however, is that cognitive aging reflects processes largely distinct from those that culminate in Alzheimer's disease or other defined dementias.

Dementia is rare in midlife, but forgetfulness and other cognitive symptoms are common. The clinician is often called upon to evaluate the seriousness of midlife cognitive symptoms, which may occur in the setting of fluctuating or declining levels of ovarian hormones, and to make recommendations regarding treatment or risk reduction. Fortunately, recent observational and experimental data are largely reassuring regarding effects of the natural menopause transition on objective measures of episodic memory and other cognitive skills. From a clinical perspective, identifying a deficit in episodic memory is an important first step to recognizing cognitive disorders that occur with age. Other worrisome features that might emerge during the patient assessment include a history of functional decline, a family history of dementia before age 60 years in a parent or sibling, or a focal abnormality on the neurological examination.

It is also important to identify factors that could affect subjective memory, even if there is no objective decline beyond that expected with age. These include cognitive aging *per se*, depression, stress effects, fatigue, hot flashes, sleep disorders, medication effects, systemic illness, and — rarely — early stages of a dementing disorder. As in other areas of medicine, prevention is the key to reducing the long-term burden of more severe forms of age-related cognitive loss. There is mounting evidence that cognitive aging can be mitigated or remediated by reducing cardiovascular risk factors, engaging in mental and physical activity, maintaining an active social network, and eating a balanced, nutritious diet that includes whole fruits and vegetables, nuts, and fish.

Summary Cognitive Function and the Menopausal Transition

There is a wealth of evidence from basic science studies that ovarian steroids regulate critical neurobiological determinants of memory and other cognitive functions. Recent evidence from a prospective study suggests that menopausal stage and hormone use impact cognitive performance. Perimenopausal women did not show the improvements in processing speed and verbal memory with repeated testing that were evident in pre- and postmenopausal women, and hormone therapy use before the final menstrual period was associated with better processing speed and verbal memory. Clinical trials show some benefit for estrogen alone therapy on verbal memory in younger postmenopausal women (< 65 years), but modest decreases in verbal memory for both younger and older women with CEE/MPA. Age, baseline cognitive performance, and formulation of hormone therapy may modulate the effects of hormone therapy on memory function. Pharmacological challenge studies show that estradiol appears to improve cholinergic function. This effect appears to be age-specific, with younger women showing benefit but older women showing no benefit or impairment. Progesterone counteracts the beneficial effects of estrogen on attention and speed after cholinergic blockade. Clinical studies demonstrate that serious cognitive disorders such as Alzheimer's disease are rare during the perimenopausal and early postmenopausal stage. Regardless of age, however, a clinical evaluation should be conducted if cognitive declines are associated with a significant decline in daily function.

Clinical and Research Priorities

Routine evaluation of depressive symptoms in perimenopausal women is warranted by the finding that the perimenopausal stage represents a window of vulnerability to mood disorders. Routine evaluation is made easy in the clinical setting by the availability of quick and validated screening tools such as the PHQ-9, which is accessible on-line and is free of charge. By implementing routine screening for depression into their clinical practice, menopausal health practitioners can play a primary role in the prevention and treatment of depressive disorders

in perimenopausal women. A similar screen for cognitive disorders is not warranted by the available data, as the risk of cognitive dysfunction is rare and the magnitude of cognitive change across the transition is small.

An important priority for future investigations is identifying which women may be at risk for cognitive and mood disorders across the menopausal transition. Clinical trials could then target those phenotypes. Past history of a depressive disorder, severe climacteric symptoms, and psychosocial stressors increase risk for depression at this life stage, but the risk is evident even when those factors are controlled. Estradiol levels do not predict who is at risk for depression, but estradiol has been shown to be effective in treating perimenopausal depression. Genetic studies may prove helpful in identifying vulnerable women and guiding future intervention trials. Non-human primate studies suggest that depression may be a risk factor for CHD, so early intervention may prevent CHD. Women with a large number of physiological hot flashes appear to be vulnerable to memory dysfunction, but future studies are needed to further characterize this relationship.

Issues related to the measurement of cognitive change in midlife complicate our understanding of the magnitude of cognitive changes in the menopausal transition. Prospective studies require repeated assessments with standardized neuropsychological tests, and midlife women show significant practice effects on such tests. Therefore, studies require large sample sizes and the use of memory tests on which it is difficult to reach maximum performance. Neuroimaging studies, including resting positron emission tomography and functional magnetic resonance imaging during cognitive tasks, may be helpful in identifying biomarkers of cognitive vulnerability in midlife women. To date there are no prospective neuroimaging studies of women as they transition through the menopause. Pharmacologic challenge studies have been helpful in identifying which women may be susceptible to mood disorders during the menopausal transition, and this approach may also help to identify subsets of women who are especially susceptible to cognitive dysfunction.

Through continued research we can better identify who is at risk for depressive symptoms and cognitive decline in the menopausal transition and guide treatment decisions.

Acknowledgments

Source of Funding: The project described was supported by Award Number R13AG033944 from the National Institute on Aging. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute on Aging or the National Institutes of Health.

References

1. Heiskanen TH, Niskanen LK, Hintikka JJ, et al. Metabolic syndrome and depression: a cross-sectional analysis. *J Clin Psychiatry* 2006;67(9):1422–7. [PubMed: 17017829]
2. Cizza G, Primma S, Csako G. Depression as a risk factor for osteoporosis. *Trends Endocrinol Metab* 2009;20(8):367–73. [PubMed: 19747841]
3. Perez-Lopez FR, Chedraui P, Gilbert JJ, Perez-Roncero G. Cardiovascular risk in menopausal women and prevalent related co-morbid conditions: facing the post-Women's Health Initiative era. *Fertil Steril* 2009;92(4):1171–86. [PubMed: 19700149]
4. National Institutes of Health State-of-the-Science Conference statement: management of menopause-related symptoms. *Ann Intern Med* 2005;142(12 Pt 1):1003–13. [PubMed: 15968015]
5. Freeman EW, Sammel MD, Liu L, Gracia CR, Nelson DB, Hollander L. Hormones and menopausal status as predictors of depression in women in transition to menopause. *Archives of General Psychiatry* 2004;61(1):62–70. [PubMed: 14706945]

6. Freeman EW, Sammel MD, Lin H, Nelson DB. Associations of hormones and menopausal status with depressed mood in women with no history of depression. *Arch Gen Psychiatry* 2006;63(4):375–82. [PubMed: 16585466]
7. Cohen LS, Soares CN, Vitonis AF, Otto MW, Harlow BL. Risk for new onset of depression during the menopausal transition: the Harvard study of moods and cycles. *Arch Gen Psychiatry* 2006;63(4):385–90. [PubMed: 16585467]
8. Bromberger JT, Matthews KA, Schott LL, et al. Depressive symptoms during the menopausal transition: the Study of Women's Health Across the Nation (SWAN). *J Affect Disord* 2007;103(1-3):267–72. [PubMed: 17331589]
9. Schmidt PJ, Haq N, Rubinow DR. A longitudinal evaluation of the relationship between reproductive status and mood in perimenopausal women. *Am J Psychiatry* 2004;161(12):2238–44. [PubMed: 15569895]
10. Ryan J, Burger HG, Szoek C, et al. A prospective study of the association between endogenous hormones and depressive symptoms in postmenopausal women. *Menopause* 2009;16(3):509–17. [PubMed: 19169164]
11. Soares CN, Almeida OP, Joffe H, LS C. Efficacy of estradiol for the treatment of depressive disorders in perimenopausal women: a double-blind, randomized, placebo-controlled trial. *Archives of General Psychiatry* 2001;58(6):529–34. [PubMed: 11386980]
12. Cohen LS, Soares CN, Poitras JR, Prouty J, Alexander AB, Shifren JL. Short-term use of estradiol for depression in perimenopausal and postmenopausal women: a preliminary report. *Am J Psychiatry* 2003;160(8):1519–22. [PubMed: 12900318]
13. Harsh, VL.; Fortinsky, P.; Gearhart, TF.; Rubinow, DR.; Schmidt, PJ. Effects of induced hypogonadism on mood and behavior in healthy women. American Psychiatric Association; Washington DC: 2008.
14. Warnock JK, Bundren JC, Morris DW. Depressive symptoms associated with gonadotropin-releasing hormone agonists. *Depress Anxiety* 1998;7(4):171–7. [PubMed: 9706454]
15. Steingold KA, Cedars M, Lu JK, Randle D, Judd HL, Meldrum DR. Treatment of endometriosis with a long-acting gonadotropin-releasing hormone agonist. *Obstet Gynecol* 1987;69(3 Pt 1):403–11. [PubMed: 2950349]
16. Kessler RC, McGonagle KA, Swartz M, Blazer DG, Nelson CB. Sex and depression in the National Comorbidity Survey. I: Lifetime prevalence, chronicity and recurrence. *J Affect Disord* 1993;29(2-3):85–96. [PubMed: 8300981]
17. Diagnostic and Statistical Manual of Mental Disorders. Fourth. Washington, DC: American Psychiatric Association; 1994.
18. Pignone MP, Gaynes BN, Rushton JL, et al. Screening for depression in adults: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med* 2002;136(10):765–76. [PubMed: 12020146]
19. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. *Jama* 1999;282(18):1737–44. [PubMed: 10568646]
20. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001;16(9):606–13. [PubMed: 11556941]
21. Lowe B, Unutzer J, Callahan CM, Perkins AJ, Kroenke K. Monitoring depression treatment outcomes with the patient health questionnaire-9. *Med Care* 2004;42(12):1194–201. [PubMed: 15550799]
22. Avis NE, Crawford S, Stellato R, Longcope C. Longitudinal study of hormone levels and depression among women transitioning through menopause. *Climacteric* 2001;4(3):243–249. [PubMed: 11588948]
23. Shively CA, Musselman DL, Willard SL. Stress, depression, and coronary artery disease: modeling comorbidity in female primates. *Neurosci Biobehav Rev* 2009;33(2):133–44. [PubMed: 18619999]
24. Mitchell E, Woods N. Midlife women's attributions about perceived memory changes: Observations from the Seattle Midlife Women's Health Study. *Journal of Women's Health and Gender-based Medicine* 2001;10:351–362.
25. Henderson V, Guthrie J, Dudley E, Burger H, Dennerstein L. Estrogen exposures and memory at midlife: A population-based study of women. *Neurology* 2003;60:1369–71. [PubMed: 12707448]

26. Fuh JL, Wang SJ, Lee SJ, Lu SR, Juang KD. A longitudinal study of cognition change during early menopausal transition in a rural community. *Maturitas*. 2005
27. Meyer PM, Powell LH, Wilson RS, et al. A population-based longitudinal study of cognitive functioning in the menopausal transition. *Neurology* 2003;61(1):801–806. [PubMed: 14504324]
28. Greendale GA, Huang MH, Wight RG, et al. Effects of the menopause transition and hormone use on cognitive performance in midlife women. *Neurology* 2009;72(21):1850–7. [PubMed: 19470968]
29. Maki PM. Menopause and cognition. In: RA, L., editor. *Treatment of the postmenopausal woman: Basic and clinical aspects*. 3rd. San Diego, CA: Academic Press; 2007. p. 279-93.
30. Maki PM, Sundermann E. Hormone therapy and cognitive function. *Hum Reprod Update*. 2009
31. Joffe H, Hall JE, Gruber S, et al. Estrogen therapy selectively enhances prefrontal cognitive processes: a randomized, double-blind, placebo-controlled study with functional magnetic resonance imaging in perimenopausal and recently postmenopausal women. *Menopause* 2006;13(3):411–22. [PubMed: 16735938]
32. Linzmayer L, Senglitsch HV, Saletu B, et al. Double-blind, placebo-controlled psychometric studies on the effects of a combined estrogen-progestin regimen versus estrogen alone on performance, mood and personality of menopausal syndrome patients. *Arzneimittelforschung* 2001;51(3):238–45. [PubMed: 11304940]
33. Tierney MC, Oh P, Moineddin R, et al. A randomized double-blind trial of the effects of hormone therapy on delayed verbal recall in older women. *Psychoneuroendocrinology* 2009;34(7):1065–74. [PubMed: 19297102]
34. Espeland M, Rapp S, Shumaker S, et al. Conjugated equine estrogens and global cognitive function in postmenopausal women: Women's Health Initiative Memory Study. *JAMA* 2004;291(24):2959–68. [PubMed: 15213207]
35. Viscoli CM, Brass LM, Kernan WN, Sarrel PM, Suissa S, Horwitz RI. Estrogen therapy and risk of cognitive decline: results from the Women's Estrogen for Stroke Trial (WEST). *Am J Obstet Gynecol* 2005;192(2):387–93. [PubMed: 15695976]
36. Dumas J, Hancur-Bucci C, Naylor M, Sites C, Newhouse P. Estrogen treatment effects on anticholinergic-induced cognitive dysfunction in normal postmenopausal women. *Neuropsychopharmacology* 2006;31(9):2065–78. [PubMed: 16482084]
37. Dumas J, Hancur-Bucci C, Naylor M, Sites C, Newhouse P. Estradiol interacts with the cholinergic system to affect verbal memory in postmenopausal women: Evidence for the critical period hypothesis. *Horm Behav* 2008;53(1):159–69. [PubMed: 17964576]