

The Menopause Transition and Cognition

Gail A. Greendale, MD; Arun S. Karlamangla, PhD, MD; Pauline M. Maki, PhD

Nearly two-thirds of women have subjective cognitive difficulties, commonly referred to as memory problems, during their menopausal transition. Symptoms also include attention or language deficits.¹ The basis for these cognitive symptoms is poorly understood; nonetheless, clinicians should have a conceptual framework to address these concerns when providing care for perimenopausal women. To build a clinically applicable approach, this JAMA Insights article will specify the definition of the menopausal transition (as distinct from postmenopause); review subjective cognitive problems in the context of other, concomitant, and possibly related, menopausal transition symptoms; and describe perceived and objectively measured cognitive function during transition and explain how they are related.

Menopause is a discrete event marked by the permanent cessation of ovarian function, diagnosed after 12 months of amenorrhea. The changeover between reproductive and nonreproductive status, which usually lasts between 4 and 10 years, is the menopausal transition, also termed *perimenopause* because it surrounds the final menstrual period. For women with previously regular menstrual cycles, early perimenopause is characterized by persistently increased cycle variability, and late perimenopause is marked by the incidence of amenorrhea for at least 60 days.²

Vasomotor symptoms (VMS, eg, hot flashes or night sweats), depressive symptoms, anxiety symptoms, and sleep disturbance are referred to as *menopause symptoms* but actually begin in early perimenopause and worsen in the later menopausal transition.^{3,4} It has been recognized that other conditions such as cognitive problems can increase during the menopausal transition.³ Knowledge of how perceived cognitive difficulties correspond with objectively measured ones, the duration of menopausal transition-related cognitive symptoms, and associations between cognition and other common menopausal transition-associated concerns is incomplete, but what is known can inform clinical care.

Subjective Cognitive Difficulties and Their Associations With Objective Cognitive Performance

In a cross-sectional analysis of a population-based cohort (N = 230), 62% of women reported subjective cognitive problems during the menopausal transition. Examples included difficulty retrieving words or numbers, forgetting the purpose of a behavior (eg, entering a room and not knowing why), losing one's train of thought, and overlooking appointments.¹

While cross-sectional clinical studies of pre-, peri- and postmenopausal women showed intact cognitive test performance (ie, scores within normative ranges), groups of perimenopausal women reported more subjective cognitive difficulties than did premenopausal or postmenopausal groups.⁴ Additionally, subjective cognitive difficulties in perimenopausal women were associated with lower objective test results. For example, a cross-sectional study of 130 perimenopausal women found that those who reported frequent forgetting had lower (though still normative) scores on a measure of attention.⁵ Another cross-sectional study of 75 perimenopausal women reported that the degree of perceived memory difficulty was related to worse performance on tests of working memory and complex attention, and that greater depressive, anxiety, somatic, and sleep disturbance symptoms were associated with more perceived memory problems.⁶ While self-reported VMS have not been convincingly linked with cognitive test results, objectively measured VMS have been associated with poorer verbal memory performance.⁷

Longitudinal examinations of cognitive performance, measured as women advance through the menopausal transition, find small but statistically significant negative effects of the menopausal transition.^{3,8,9} Analyses from a large longitudinal cohort (N ≈ 2000) revealed a temporary decrement in cognitive processing speed, verbal encoding (immediate paragraph recall), and verbal episodic memory (delayed paragraph recall) during perimenopause, which resolved in the postmenopausal period.^{3,8} The negative perimenopause effect was subtle and confined to the absence of a learning effect. The expected improvement in scores with repeated administration of the tests was absent, but scores did not decline. When VMS, anxiety, depression, and sleep symptoms were added to models of menopausal transition stage and cognition, the negative association between perimenopause and learning was unaltered.³ Another cohort study (N ≈ 400) found that encoding (immediate recall) of a word list was lower in postmenopause compared with premenopause and that verbal memory (delayed recall) declined in perimenopause compared with premenopause. Postmenopausal observations were too few to confidently determine whether the verbal memory decline continued during postmenopause.⁹ Anxiety, depressive, and stress symptoms were not associated with cognitive performance in this analysis, nor did adjusting for them alter the negative association between peri- or postmenopause and verbal encoding or memory.

Clinical Approach

Despite the limited evidence base, clinicians must address the cognitive concerns of their perimenopausal patients, especially since these symptoms may interfere with work and relationships during the transition.¹⁰ The following approaches may be used.

Normalization of the experience. During the menopausal transition, subjective cognitive deficits are common, occurring in more than half of women, and women should be reassured that this is not unusual.

Interpretation of cognitive tests. Among women with menopausal transition-related subjective cognitive symptoms, scores on one-time measures of cognitive performance will usually fall within normative range. However, this does not invalidate the patient's self-assessment, which likely reflects her perception of a diminution from prior performance. When repeated over time, objective cognitive tests do show subtle deficits, but there is no agreement regarding the persistence of these deficits. There may be a transient perimenopausal learning decrement (test scores do not improve with repeated administrations, as is expected in middle age),

Table. The Menopausal Transition and Cognition—An Approach to Patient Education

Examples of Patient Questions	Examples of Clinician Responses
I'm having memory problems (eg, forgetfulness, difficulty retrieving names, losing train of thought). Is this part of menopause?	This is a common symptom. About half of women experience forgetfulness and other cognitive problems as a part of their menopausal transition. ^a
Are other menopausal transition symptoms (eg, hot flashes, poor sleep, and feelings of anxiety or depression) responsible for the memory difficulties?	Although menopausal transition symptoms are associated with cognitive difficulties, changes in cognition across menopause stages occur independently of those symptoms. Cognitive difficulties can occur in women without any other menopausal transition symptoms.
If I treat my other menopausal transition symptom(s), will my memory problems improve?	There is general evidence (in circumstances other than the menopausal transition) that treating depression, anxiety, and sleep disturbance improves memory. No studies directly address whether treating these symptoms during the menopausal transition improves cognition. Treating your other menopausal transition symptom(s) may or may not have a cognitive benefit. ^b
Are the (menopausal transition-related) cognitive symptoms a sign that I am developing dementia?	Dementia is very rare at midlife unless a person has a family history of early-onset Alzheimer disease. In one study, mild cognitive test effects seen in the menopausal transition resolved in postmenopause. Another study showed that difficulty remembering words persisted in postmenopause, but verbal memory test scores remained well within the normal range.
Should I have my memory tested?	In most cases, testing is not necessary. However, if your cognitive symptoms are significantly interfering with your daily life, a referral for a neuropsychological evaluation could be helpful in determining the nature and severity of the problem. ^c
Are there any nonpharmacological things I can do to manage my cognitive symptoms during the menopause?	Mild attention deficits contribute to misplacing keys, forgetting a parking spot, or not registering the name of a new acquaintance. This can be mitigated by focusing attention (eg, consciously landmarking the car location) and using mnemonic devices (eg, repeating new names aloud). Physical activity and control of cardiometabolic risk factors are possible strategies to prevent cognitive decline, but whether they improve menopausal transition-related cognitive symptoms is unknown. ⁴

^a Assess for other conditions that can affect cognitive function such as anxiety and depressive or sleep disorders. These symptoms are common during the menopausal transition and can have independent effects on cognition. If present, discern whether they are clinically meaningful and warrant treatment or a consultation with a clinician with the requisite expertise.

^b Assess the severity and impact of other symptoms and the patient's desire for intervention (with possible side benefit on cognition). There is preliminary evidence that treating hot flashes benefits cognitive function, but more research is needed.

^c Women report that cognitive symptoms can interfere with work and relationships.¹⁰ However, clinically significant functional impairment, such as a decrement in job performance or problems managing daily activities, would be unusual in association with menopausal transition-related cognitive symptoms and would merit consultation.

or there may be a small, fixed, absolute cognitive decline from pre- to postmenopause.^{3,8,9} Usually there is no clinically significant functional impairment associated with these small-magnitude objective test changes. Consideration of referral for neuropsychiatric consultation is appropriate if the patient reports that her symptoms interfere with her ability to function in daily life. Dementia in the menopausal transition age range is rare.

Interface between menopausal transition symptoms and cognition. Menopausal transition-related cognitive decrements are not associated with VMS, sleep disturbance, anxiety, or depressive symptoms. However, objectively measured hot flashes, greater anxiety, subclinical depressive symptoms, and clinical depression are independently associated with poorer cognitive performance during the menopausal transition. Thus inquiring about these

symptoms, and treating them if clinically warranted, should be part of the clinical approach.^{3,4}

Treatment. For menopausal transition-related subjective cognitive symptoms, patient education often suffices. The Table lists questions that patients may ask and an approach to respond, based on the authors' clinical interpretation of the available evidence. No trials support the use of hormone therapy during the menopausal transition solely for subjective cognitive difficulties, nor are there trials that examine whether treating menopause symptoms benefits cognitive function. Nevertheless, patients do seek symptom relief, and lessening VMS with hormone therapy or selective serotonin reuptake inhibitors may improve cognitive function. Improving sleep, using mnemonic devices, or engaging in physical activity may also lessen menopausal transition-related cognitive difficulties.

ARTICLE INFORMATION

Author Affiliations: Department of Medicine, Division of Geriatrics, University of California, Los Angeles (Greendale, Karlamangla); Departments of Psychiatry, Psychology, and Obstetrics and Gynecology, University of Illinois at Chicago (Maki).

Corresponding Author: Gail A. Greendale, MD, Department of Medicine, Division of Geriatrics, University of California, Los Angeles, 10945 Le Conte Ave, Ste 2339, Los Angeles, CA 90095 (ggreenda@mednet.ucla.edu).

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