Case:
A 49-year-old woman whose last menses occurred 3 months ago is now concerned about recent forgetfulness and trouble multitasking. Her mother, who is 80 years old, was diagnosed last year with Alzheimer disease, and the patient is concerned about her risk for dementia. How would you counsel her?

Management issues by:

The patient’s concerns relate to aging (impending loss of fertility), cognitive symptoms (forgetfulness and difficulty multitasking), and a serious age-related disorder (Alzheimer disease). Three facts should inform the initial approach. First, cognitive complaints are common. Second, dementia during midlife is rare. Third, many factors associated with cognitive symptoms are eminently treatable.

Cognitive complaints are always worrisome, but the clinical significance varies with the age of the patient. Alzheimer disease and other forms of dementia are rare before age 65, so the a priori likelihood that this patient’s symptoms represent early Alzheimer disease is quite low. The family history of late-onset Alzheimer disease does not change this calculus, although she faces a modest elevation in risk during old age.

In midlife, cognitive difficulty is associated with a variety of factors, most of which are not especially ominous. It is important to recognize that cognitive skills fall off modestly with “normal” aging. Some people are more astute in recognizing these subtle changes. Other considerations are described below.

The first step is to evaluate whether there is a clinically significant loss of memory or other cognitive abilities.1 Warning signs include 1) family history of dementia beginning before age 60 years, 2) poor memory manifested by repeating questions and forgetting recent events even when reminded or prompted, and 3) functional impairment at work or home. A reliable informant is essential for the determination of memory loss or functional decline. Short screening batteries such as the Mini-Mental State Examination are of little value when symptoms are subtle, but normal findings can be reassuring. More detailed neuropsychological assessment is unnecessary unless warning signs are present. When in doubt, consultation by a neurologist or other dementia specialist is more cost effective than ordering structural (computed tomography or magnetic resonance imaging) or functional (positron emission tomography) brain imaging, “screening” blood tests, and neuropsychological testing.
If it appears likely that cognitive concerns are unaccompanied by evidence for cognitive impairment, the second step is to consider medical, psychological, and social factors that may underlie the patient’s symptoms.1

Depressed mood is by far the most common factor linked to cognitive symptoms. A variety of midlife stressors can affect mood and might affect cognitive efficiency independently of mood. These include vasomotor symptoms, sleep disturbances, empty-nest syndrome (or adolescent children!), career demands, marital friction, and financial challenges. In this particular instance, there is the added stress of an older, perhaps no longer autonomous, parent with Alzheimer disease. Medical disorders (thyroid disease, for example), cognitive adverse effects of prescription medications, and excessive alcohol consumption are other possibilities. What is important is that there are effective interventions for each of these considerations.

**What about hormone therapy?**

Fluctuations in circulating levels of estradiol and progesterone that accompany the natural menopause transition and the decline that follows, at least theoretically, have the potential to affect the brain and cognitive performance. In ovariectomized laboratory animals, estradiol improves performance on specific cognitive tasks. Human data, derived largely from women undergoing natural menopause at a usual age, are less convincing. Serum estradiol levels show little relation to cognitive abilities,2 and the preliminary report from a large randomized clinical trial in younger postmenopausal women suggests no important cognitive benefit (or harm) of transdermal estradiol or oral conjugated estrogens.3 (Data from another large, recently completed trial are not yet available.) In older postmenopausal women (aged 65+ years), estrogen-containing hormone therapy may increase dementia risk, but there is no evidence for an increased risk of Alzheimer disease when hormone therapy is initiated and used during the menopausal transition or early postmenopause.4

Assuming that objective cognitive loss is not present, I see no contraindication to hormone therapy in this patient, particularly if vasomotor symptoms contribute to cognitive symptoms through sleep disruption or through stress caused by reductions in her quality of life. Evidence is insufficient to recommend hormone therapy specifically to enhance cognitive function, and there is no FDA-indication for this purpose.

**Counseling**

I would first make sure the warning signs mentioned above are not present. This being the case, I would be comfortable in offering firm reassurance that the patient’s symptoms are not a premonition of looming Alzheimer disease and begin to explore factors—medical, psychological, and social—for which interventions might make a difference.

Finally, I would counsel her on things she might do proactively to reduce her risk of future Alzheimer disease, although conclusive evidence is lacking. These fall into two overlapping categories: vascular risk reduction and lifestyle change. Risk factors for vascular disease are also risk factors for Alzheimer disease, including hypertension, hyperlipidemia, diabetes, obesity, and smoking. If these conditions are present, the patient should be encouraged to work with her healthcare providers to achieve optimal control.

Also, risk is probably reduced by common sense lifestyle modifications, such as regular aerobic activity (eg, brisk walking 30 minutes a day, 5 days a week), mental activity, social engagement, and good nutrition (eg, 5 daily servings of whole vegetables and fruits; 2 or 3 weekly servings of fish such as salmon, high in polyunsaturated fatty acids). Of these, evidence is best developed for aerobic activity, and it is here that I would place the strongest emphasis.

**Disclosure:** Dr. Henderson reports: none.

**References**


**Question:**
A healthy 53-year-old woman, recently menopausal, presents to discuss her bone density test. She recently received information along with her normal mammogram letter about osteoporosis screening and an invitation to have a dual-energy x-ray absorptiometry (DXA). She presents today with her DXA showing a T-score of –1.9 in the femoral neck and –2.1 in the spine. She has done some online reading and understands that she has osteopenia, and she would like to discuss treatment options.

**Commentary by:**

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There are four important questions to answer about this woman:
1. Was a bone density test indicated?
2. What is important to tell this patient about bone health and the diagnosis of osteopenia?
3. Is treatment indicated, and if so what treatment?
4. When would a repeat DXA be appropriate?

Answers:
1. In recent years, the focus of health care in our patients has changed from disease treatment to disease prevention. This is particularly true in the arenas of cardiovascular disease, diabetes, Alzheimer disease, and osteoporosis. Patients are encouraged to take a proactive approach to their health and are typically interested in screening tests. Women are aware of osteoporosis and the risk of fracture, and screening with a noninvasive, painless, low-cost test makes intuitive sense. However, in the case of a 52-year-old newly menopausal woman, was the test indicated?

Current guidelines from the National Osteoporosis Foundation1 and The North American Menopause Society2 state that the following groups of women should be screened:
- Women aged 65 years and older
- Women aged younger than 65 years who are at high risk for fracture
- Adults with fracture when aged older than 50 years
- Adults with a medical condition or who are taking a medication that is associated with low bone mass

This woman did not meet criteria for screening. According to published data by Schnatz and colleagues,3 41% of 612 women who had been referred for and underwent DXA screening did not meet criteria for screening.

2. Although the DXA was not indicated in this woman, we are now faced with a patient who has documented osteopenia (T-score between –1.0 and –2.5) and has questions. The most important first step in management of this patient is education about bone physiology and universal bone health guidelines. Peak bone mass in women is achieved at approximately age 35 years, and bone loss declines after that age at an average rate of 0.5% to 1% per year. Bone loss accelerates for the 5 to 7 years around the menopause transition. During that time, women can lose bone at a rate of up to 2% per year and a total of 20% of their bone during that time. All women, but
especially this newly menopausal patient, should be encouraged to focus on lifestyle measures to slow further bone loss. This includes adequate calcium and vitamin D, preferably from food instead of supplements (current recommendations are 1,200 mg calcium per day and 600 IU-800 IU of vitamin D₃ per day), weight-bearing exercise (30-45 minutes per day), avoidance of smoking, and limited alcohol intake.

3. Pharmacologic treatment is not indicated in this woman specifically for her bone. However, if she is symptomatic with vasomotor symptoms related to her menopause transition, hormone therapy might be considered for symptom management. Such therapy would have a positive effect on her bone.

It is important to emphasize to this woman that although she has osteopenia, age is a key risk factor in determining fracture risk. A young 53-year-old woman with osteopenia has a vastly lower risk of fracture compared with a 73-year-old woman with the same T-score. Given our current understanding of fracture risk and our more recent understanding of the risk of long-term bisphosphonate therapies, pharmacologic treatment is indicated only for those patients at high risk of fracture.

According to the National Osteoporosis Foundation (NOF) 2013 Guidelines, pharmacologic treatment should be initiated in postmenopausal woman and men aged 50 years and older with:
- T-score ≤–2.5 (excluding secondary causes) by DXA of femoral neck or spine
- Hip or vertebral fracture
- Low bone mass and 10-year probability of hip fracture ≥3%, or 10-year probability of any major osteoporosis-related fracture ≥20% (FRAX)

According to NOF guidelines, FRAX calculation is indicated in this patient. Using the FRAX online calculator, this woman has a 10-year risk of 6% for a major osteoporotic fracture at any location and a 10-year risk of 0.7% for hip fracture. These values are well below the NOF treatment guidelines of a 10-year risk of greater than 20% for a major osteoporosis-related fracture and a greater than 3% 10-year risk for hip fracture. Given the FRAX calculation result for this woman, she should be encouraged to follow the universal bone health guidelines discussed above.

4. This woman does not need a repeat DXA until age 65 years unless she has a significant change in her health history that would affect her bone health (ie, being started on chronic prednisone for asthma). Although she currently has osteopenia and is likely to be in a phase of accelerated bone loss (early postmenopausal period) for the next several years, she is unlikely to meet FRAX criteria for pharmacologic treatment or develop osteoporosis before age 65 years.

It should be emphasized to this patient that a healthy lifestyle, including a diet rich in calcium and vitamin D, exercise, limitation in alcohol intake, and avoidance of smoking are the most important things she can do for her bone health.

Disclosure: Dr. Larkin reports: Speaker’s Bureau: Shionogi Inc.; Advisory Board: Pfizer.

References
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