



## 1. Dementia and Family History



Question:

**What is a significant family history for dementia, and when should you refer for genetic testing? What are the current tests?**

David Hogan, MD, FACP,  
FRCPC, geriatric medicine,  
replies.

Response:

Both genetic and non-genetic factors can either cause or increase the susceptibility to dementia. Dementia is a genetically complex group of disorders. There are cases of familial frontotemporal dementia (FTD-17) and vascular dementia.

Genetic susceptibility risk factors for Alzheimer's disease (AD) have been identified. The best documented one is the apolipoprotein epsilon 4 located on chromosome 19. A small number of cases of AD (< 5%) are familial and arise from a genetic mutation. Causative mutations have been found on chromosome 1 (presenilin 2), chromosome 14 (presenilin 1), and chromosome 21 (genes that encode for amyloid precursor protein). Typically with familial AD, the onset of dementia occurs

earlier than what is seen in sporadic AD, and there is a family history very suggestive of autosomal dominant inheritance (about half of every generation is affected).

A family history should be obtained on everyone presenting with a dementia. For over 95% of families with dementia, there is no test or biomarker that can accurately predict on an individual basis who will develop dementia. If an autosomal dominant mode of inheritance is suspected, a referral to a genetics clinic would be a consideration. If a family specific genetic mutation has been identified, predictive genetic testing may be an option for unaffected individuals. This test would be best performed through a genetics clinic.

## 2. Estrogen Therapy



### Question:

**What is the role of hormonal therapies post-WHI in the management of osteoporosis? How will the arrival of parathyroid hormone influence the management of osteoporosis?**

Greg Kline, MD, FRCPC, endocrinologist, replies.

### Response:

Estrogen therapy in post-menopausal women has been a controversial issue since the Women's Health Initiative (WHI). Prior to this, several epidemiologic studies appeared to show estrogen prevented osteoporosis and fractures in post-menopausal women. The WHI (premarin plus Provera® versus placebo) was not designed to address the issue of osteoporosis, although incident fractures were recorded as a secondary outcome. The results indicated a significant reduction in vertebral and hip

fractures, with increasing benefit seen in prolonged use of estrogen.



Study authors tried to balance the potential good effects of estrogen versus potential bad effects by generating a global risk index that combined both. This analysis suggested that adverse effects of hormone replacement therapy outweighed the potential benefit.

Estrogen therapy is still considered useful for the management of estrogen withdrawal syndromes, with a preference for short-term use (< 2 years). The Canadian Osteoporosis Management Guidelines (2002) consider estrogen a first-line option for

prevention and a second-line option for treatment.

Daily subcutaneous parathyroid hormone (PTH 1-34) is a true "bone anabolic" agent found to dramatically increase bone mineral density, and reduce vertebral fractures in several prospective trials. Ideally, it would be given for one to two years followed by anti-resorptive therapy. While many experts see PTH 1-34 as revolutionizing the treatment of osteoporosis, there is no evidence it is more effective than standard anti-resorptive therapy. There is no consensus as to who may benefit the most, which is very relevant, as therapy costs will likely be extremely high.

#### Suggested Readings

1. Roussow JE, Anderson GL, Prentice RL, et al: Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative Randomized Controlled Trial. *JAMA* 2002; 288(3):321-33.
2. Brown JP, Josse RG: 2002 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada. *CMAJ* 2002; 167(10 suppl):S1-34.
3. Neer RM, Arnaud CD, Zanchetta JR, et al: Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med* 2001; 344(19):1434-41.