



Basic Facts for the Primary Care Physician on Hormone Replacement Therapy (HRT) as a Preventive Strategy for Dementia in Women and Men

1. Overview for Hormone Replacement Therapy in Women

Estrogen and progesterone are powerful, psychoactive substances with receptors located in the hippocampus and the basal forebrain. Some women who undergo oophorectomy for other medical purposes during midlife demonstrate transient neuropsychological deficits after surgical removal of the gonads. The relationship between endogenous estrogen levels and risk for cognitive decline in older women remains controversial (1), (2), (27). Transgenic rodent models of Alzheimer's disease demonstrate that estrogen levels may play some role in the deposition of amyloid within the brain (2).

Hormone replacement therapy (HRT) to prevent senescent memory loss or functional decline is controversial. Many studies have identified cognitive benefits from these medications in postmenopausal women while others demonstrate no improvement (**See Table 1**). Serious health consequences are reported with HRT, such as increased risk for deep venous thrombosis, hemorrhagic stroke and others (3), (4). Potential beneficial effects from hormone replacement therapy include suppression of menopausal symptoms, e.g., hot flashes, as well as slowing of osteoporosis (5).

The interpretation of scientific studies on hormone replacement treatment is complicated by several issues. First, which kind of hormone preparation is best suited for cognitive protection and does that preparation produce excessive morbidity or mortality in at-risk individuals? Second, at what age does initiation of HRT provide optimal protection for dementia? Some studies suggest that early treatment is beneficial while others cannot draw specific conclusions on this matter. Third, how long should treatment continue? Some studies suggest that treatment limited to the perimenopausal period may provide the best benefit. Other studies cannot substantiate that observation. Fourth, are there subgroups of individuals who would benefit from hormone replacement treatment? For instance, does the presence of a strong family history of Alzheimer's disease, APOE 4 alleles, hypertension, metabolic syndrome or

other potential risk factors increase the likelihood that estrogen will provide beneficial results in women? Fifth, are some women at excessive risk for complications from HRT as a “dementia prevention”?

Table 1. A Summary of Recent Studies on the Role of Hormone Replacement Therapy on Cognitive Function

| No. | t | a | n | Hormone | Outcome from Replacement Therapy | Refs. |
|-----|---------|-----|-------|---------|--|-------|
| 1 | CS | 65+ | 2816 | Mixed | ↓ Dementia risk | 9 |
| 2 | 4.2 yr. | 65+ | 4894 | Mixed | NC - dementia, few side effects | 10 |
| 3 | 4 yr. | 65+ | 13807 | Mixed | No benefit for cognition | 11 |
| 4 | 5yr. | 50+ | 103* | Mixed | Possible benefit in verbal memory for non-demented women | 12 |
| 5 | CS | 75+ | 3924 | Mixed | No cognitive benefit | 13 |
| 6 | 1 yrs | 65+ | 4532 | Mixed | ↑ Risk of dementia, NC-MCI | 14 |
| 7 | 16 | 50+ | 472 | ERT | ↓ Risk for AD | 15 |
| 8 | 1-5 | 65+ | 1124 | ERT | ERT delayed onset of dementia and decreased risk | 16 |

t= study of duration *Matched Study, mixed variable - mixture of estrogen and progestin
 NC- no change CS-cross-sectional a=age of entry
 Mixed - estrogen and progestin of variable doses and mixture
 ERT- estrogen replacement therapy

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2. Longitudinal Studies

Over 30 studies have examined the role of estrogen levels, perimenopausal events, and hormone replacement therapy on the risk for developing dementia (6), (26). Multiple, longitudinal studies have failed to conclusively determine the role of HRT in the prevention of Alzheimer’s disease (**See Table 1**). The preponderance of recent data suggests that hormone replacement therapy does not provide a significant protective benefit to women. The Agency for Health Care Research and Quality examined this issue and concluded that hormone replacement therapy was not proven to be beneficial for long-term cognitive function (29). The possibility remains that responsive subgroups exist within populations of aging women who may benefit from HRT.

3. Potential Toxicity of HRT Therapy in Women

Potential toxicity of HRT includes cardiovascular, biliary disease and stroke. The effect of HRT on coronary artery disease (CAD) remains controversial; however, there may be a “protective” effect on heart function (3). Risk for breast cancer remains controversial (5). Increased rates of mortality are reported with some forms of HRT and some variable benefit on bone density (**See Table 2**), (3).

Table 2. Major Complication of HRT in Post-Menopausal Women (3), (5), (8)

| Potential Complication | Conventional Wisdom | Study Results |
|-------------------------|---------------------|------------------------------|
| Breast Cancer | NC or SL↓ | 10 observation studies |
| Stroke | ↑ Risk | Over 4 studies |
| Coronary Artery Disease | Undetermined | Multiple conflicting studies |
| Deep Venous Thrombosis | ↑ Risk | Multiple conflicting studies |
| NC – no change | | |

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4. Clinical Recommendations

Although lower estradiol levels in older women may be related to decreased cognitive function in later life (27), physicians should not recommend HRT as a preventive intervention for Alzheimer's disease or other types of dementia. The risk-benefit ratio for HRT exceeds the uncertain benefit from this intervention; however, women receiving HRT to suppress perimenopausal symptoms or prevent osteoporosis may enjoy a small cognitive benefit from the medication (5), (6), (7), (16).

The effect of HRT on the risk of developing other forms of dementia, especially vascular dementia and diffuse Lewy body disease has not been evaluated. The slightly increased risk among older females for developing Alzheimer's disease beyond age-adjusted rate of survival has not been proven to depend on differences in hormonal content.

The identification of groups with specific sensitivity to hormone replacement therapy might enhance the therapeutic selection process and reduce the risk to patients. This type of selective targeting awaits further research on the dementias. Other variables such as exercise, or genetic features, such as APOE typing, may play some role in predicting outcomes from therapy.

Hormone Replacement Therapy in Men

1. Overview of HRT for Men

The use of testosterone in aging males has increased 500% since 1994 and 30% in the year from 2003 to 2004 (17). The probable risk to older patients for prescription of endogenous testosterone is low; however, the cognitive benefit has not been conclusively proven (17), (18).

Several studies have examined the role of testosterone on the risk and pathogenesis of Alzheimer's disease (**See Table 3**). Male andropause is described as a potential cause of some age-related brain pathology. Diminished levels of testosterone in men have been associated with increased risk for developing dementia in later life. Dietary supplementation of testosterone in mice that are genetically altered to produce amyloid demonstrate diminished amyloid load in medicated rodents. Rodent studies suggest that testosterone may alter the production and metabolism of amyloid in the brains of transgenic mice (19), (23). Post mortem studies on older human subjects demonstrate higher densities of neurofibrillary tangles and micro-infarcts in persons with lower levels of free testosterone (28).

Testosterone supplementation has potentially adverse effects on the prostate gland, although this effect remains controversial. The risk-benefit ratio for long-term supplementation of testosterone in aging men has not been determined. Testosterone supplementation has not been proven to be protective or beneficial in patients with Alzheimer's disease (24). Individuals undergoing testosterone supplementation for other medical or physiological reasons could theoretically experience some preventive benefit from this medication; however, supplementation is not recommended as a preventive intervention for older individuals, even with a family history of Alzheimer's disease. The role of testosterone in other forms of dementia, such as vascular dementia or diffuse Lewy body disease is undetermined (24).

2. The Use of Testosterone as a Neuroprotectant

The interpretation of available scientific data on the role of testosterone and cognition is complicated by several scientific obstacles. First, what dose and preparation of testosterone or combinations of male gonadal hormones are best suited to enhance cognitive function? Second, do all males respond to hormonal replacement or do specific hormone-sensitive subgroups exist that would benefit from targeted therapy? Third, what is the optimal age for initiation of therapy? Fourth, do specific disease markers, such as APOE 4

alleles or metabolic syndrome, exist that can predict at-risk group of males who benefit from testosterone therapy? Fifth, what are the long-term, i.e., 20 years, complications of testosterone supplementation on hormone-sensitive tissue such as the prostate gland? Clarification of specific groups of older individuals who are at risk for developing dementia and exhibit certain markers for hormonal sensitivity may provide targeted therapeutic interventions that enhance benefit and substantially reduce any long-term risk from hormone treatment.

Table 3
The Relationship of Testosterone Levels in Older Males and the Risk for Developing Dementia

| # | a | t | n | Outcome of Study | Ref. |
|---|-----|-------|-----|--|------|
| 1 | 65+ | CS | 310 | ↑ Serum testosterone predicts ↑ cognitive function | 20 |
| 2 | 32+ | 19 yr | 574 | ↓ Serum testosterone predicts ↑ risk of dementia | 21 |
| 3 | 65+ | CS | 210 | Low free testosterone is a predictive of AD | 22 |
| 4 | 65+ | PM | 232 | ↓ Testosterone related to ↑ NFT's and ↑ micro-infarcts | 28 |

t- duration of study CS - cross-sectional study a-age of entry n-study size
NFT-neurofibrillary tangles

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Recommendations for Primary Care Physicians

1. HRT for both men and women is an unproven intervention to slow aging or prevent dementia.
2. HRT is not recommended as a “dementia prevention” strategy for women but this treatment may benefit women who receive hormones for other specific clinical indications.
3. HRT is not recommended for older males as a form of dementia prevention therapy.
4. Future clinical research may produce specific guidelines for selection of patients and HRT preparation as well as treatment duration to reduce the risk of dementia.

References – Hormone Therapy

1. Tang MX, Jacobs D, Stern Y, et al. Effect of estrogen during menopause on risk and age at onset of Alzheimer's disease. *Lancet* 1996;348(9025):429-32.
2. Pinkerton JV, Henderson VW. Estrogen and cognition, with a focus on Alzheimer's disease. *Semin. Reprod Med.* 2005;23(2):172-9.
3. Hulley S, Furberg C, Barrett-Connor E, et al. Noncardiovascular disease outcomes during 6.8 years of hormone therapy. *JAMA* 2002;288:58-66.
4. Wasserheil-Smoller S, Hendrix SL, Limacher M, et al. Effect of estrogen plus progestin on stroke in postmenopausal women. *JAMA* 2003;289:2673-2684.
5. Peterson HB, Thacker SB, Corso PS, et al. Hormone therapy. Making decisions in the face of uncertainty. *Arch Intern Med* 2004;164:2308-2312.
6. LeBlanc ES, Janowsky J, Chan BK, Nelson HD. Hormone replacement therapy and cognition: systematic review and meta-analysis. *JAMA* 2001;285(11):1489-99.
7. Baum LW. Sex, hormones, and Alzheimer's disease. *J. Gerontol A. Biol. Sci. Med. Sci.* 2005;60(6):736-43.
8. Stevenson JC. Hormone replacement therapy: review, update, and remaining questions after the Women's Health Initiative Study. *Curr. Osteoporos Rep.* 2004;2(1):12-6.
9. Baldereschi M, Di Carlo A, Lepore V, et al. Estrogen-replacement therapy and Alzheimer's disease in the Italian longitudinal study on aging. *Neurology* 1998;50(4):996-1002.
10. Rapp SR, Espeland MA, Shumaker SA, et al. Effect of estrogen plus progestin on global cognitive function in postmenopausal women. *JAMA* 2003;289:2663-2672.
11. Kang JH, Weuve J, Grodstein F. Postmenopausal hormone therapy and risk of cognitive decline in community-dwelling aging women. *Neurology* 2004;63:101-107.
12. Maki PM, Zonderman AB, Resnick SM. Enhanced verbal memory in nondemented elderly women receiving hormone-replacement therapy. *Am J Psychiatry* 2001;158:227-233.
13. Buckwalter JG, Crooks VC, Robins SB, Petitti DB. Hormone use and cognitive performance in women of advanced age. *J Am Geriatr Soc.* 2004;52:182-186.
14. Shumaker SA, Legault C, Rapp SR, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women. *JAMA* 2003;289:2651-2662.
15. Kawas C, Resnick S, Morrison A, et al. A prospective study of estrogen replacement therapy and the risk of developing Alzheimer's disease: the Baltimore Longitudinal Study of Aging. *Neurology* 1997;48(6):1517-21.
16. Yaffe K, Grady D, Pressman A, Cummings S. Serum estrogen levels, cognitive performance, and risk of cognitive decline in older community women. *J. Am Geriatr Soc* 1998;46(7):816-21.
17. Tan RS, Salazar JA. Risks of testosterone replacement therapy in aging men. *Expert Opin Drug Saf.* 2004;3(6):599-606.
18. Hogervorst E, Bandelow S, Moffat SD. Increasing testosterone levels and effects on cognitive functions in elderly men and women: a review. *Curr Drug Targets CNS Neurol Disord.* 2005;4(5):531-40.
19. Gouras GK, Xu H, Gross RS, et al. Testosterone reduces neuronal secretion of Alzheimer's β -amyloid peptides. *PNAS* 2000;97(3):1202-1205.
20. Yaffe K, Lui LY, Zmuda J, Cauley J. Sex hormones and cognitive function in older men. *J Am Geriatr Soc* 2002;50:707-712.

21. Moffat SD, Zonderman AB, Metter EJ, et al. Free testosterone and risk for Alzheimer disease in older men. *Neurology* 2004;62:188-193.
22. Hogervorst E, Bandelow S, Combrinck M, Smith AD. Low free testosterone is an independent risk factor for Alzheimer's disease. *Exp Gerontol* 2004;39(11-12):1633-9.
23. Moffat SD. Effects of testosterone on cognitive and brain aging in elderly men. *Ann NY Acad Sci* 2005;1055:80-92.
24. Henderson VW, Hogervorst E. Testosterone and Alzheimer disease. *Neurology* 2004;62:170-171.
25. Erickson KI, Colcombe SJ, Elavsky S, et al. Interactive effects of fitness and hormone treatment on brain health in postmenopausal women. *Neurobiology of Aging* 2007;28:179-185.
26. Roberts RO, Cha RH, Knopman DS, et al. Postmenopausal estrogen therapy and Alzheimer's disease: overall negative findings. *Alzheimer Dis Assoc Disord.* 2006;20(3): 141-6.
27. Yaffe K, Barnes D, Lindquist K, et al. Endogenous sex hormone levels and risk of cognitive decline in an older biracial cohort. *Neurobiology of Aging* 2007;28:171-178.
28. Strozyk D, White LR, Petrovitch H, et al. Sex hormones and neuropathology in elderly men: The HAAS. *Neurobiology of Aging* 2007;28:62-68.
29. Agency for Healthcare Research and Quality; pharmacological treatment of dementia 2004; (97): www.AHRQ.gov/clinic.