

Consequences of Estrogen Deprivation and the Rationale for Hormone Replacement Therapy

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Presentation Summary

Menopause results in a fairly precipitous decline in estrogen levels. This estrogen deprivation is probably associated with a number of consequences, including osteoporosis, tooth loss, cardiovascular disease, stroke, age-related macular degeneration, colon cancer, diabetes mellitus, Alzheimer's disease, and Parkinson's disease. Coronary artery disease is the most frequent cause of death in women age 50 years and older, yet most women report a fear of dying from breast cancer. Current data suggest that women who take some form of hormone replacement therapy (HRT) after menopause can reduce their cardiovascular mortality approximately 50%, yet many stop taking HRT—or never start—because of this fear. Although use of estrogen replacement therapy and HRT (after a diagnosis of breast cancer)

currently is contraindicated for at least 5 years by the US Food and Drug Administration, 3 studies have found that women who took hormones had no greater incidence of breast cancer recurrence than the general breast cancer population. Evidence suggests HRT has a beneficial effect on the central nervous system, including on neurotransmitter systems within the brain that are implicated in mood disorders and depression; learning, memory, and Alzheimer's disease; and movement disorders such as Parkinson's disease.

When women are counseled about the benefits and risks of HRT and alternative therapies, it may help for physicians to keep in mind that women are more than a sum of their estrogen receptors: their emotions and beliefs will influence how they view menopause and their receptivity to available therapeutic options.

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Two types of estrogen circulate endogenously. Estradiol is the estrogen predominantly produced by a woman's ovaries during her menstruating years. After menopause, estrone, a conversion hormone that occurs from precursors made elsewhere in the body, is converted in fatty tissue. Before menopause, daily

high levels of estrogen are sustained, but these levels decline fairly dramatically in the postmenopausal interval.¹

Changes experienced after menopause may be amenable to treatment with hormone replacement therapy (HRT). The goal of such treatment is to improve the quality of life and prolong the useful, func-

tional lives for women in the interval after menopause.

Women who have had a hysterectomy can be treated with estrogen replacement therapy (ERT) because there is no endometrial target for concern about estrogen overstimulation. However, if a woman's uterus is intact, a progestin should be added to estrogen (eg, HRT) to protect against the risk of endometrial malignancy.²

Acute symptoms of menopause clearly are managed best with ERT/HRT, and there are increasing data to suggest it is important to control these symptoms not only to improve a woman's quality of life, but to reduce or eliminate hot flashes, which may prove to cause permanent damaging neurologic effects.³

Proven and probable benefits of HRT are the reduced risk of urogenital atrophy, osteoporosis, tooth loss, coronary artery disease (CAD), Alzheimer's disease, and Parkinson's disease. HRT may also help prevent adult-onset macular degeneration and colon cancer. The impact of HRT on stroke syndromes is not yet known.^{4,5}

Osteoporosis. Osteoporosis affects more than 25 million women in the United States and results in approximately 250,000 hip fractures and a total of 1.5 million fractures annually in women alone.^{6,7} Osteoporosis is the result of bone demineralization caused by accelerated bone or calcium loss. Demineralized bone is susceptible to a traumatic fracture; however, there are no symptoms until a fracture occurs.⁷

One third of white women and a quarter of African-American women will fracture their hips; what is not well known is that a quarter of white women will also fracture their spines.⁸ The costs of osteoporosis to society are estimated to be in excess of \$12 billion annually.⁹

New technologies have improved the detection of loss of bone mineral, a key predictor of osteoporotic frac-

ture. The current gold standard for measuring bone mineral density of the hip is the dual-energy x-ray absorptiometry scan.¹⁰ The benefits of ERT/HRT as both prevention and treatment of osteoporosis are well established. The National Osteoporosis Foundation Guidelines for the assessment, diagnosis, prevention, and treatment of osteoporosis identify HRT as first-line therapy.¹¹

The effect of ERT/HRT on hip and spinal fractures in women is also important. Case-controlled studies have shown that ERT/HRT can reduce the incidence of these fractures to approximately one half what they would be with no therapy.¹² This translates to significant healthcare savings and strongly contributes to a woman's quality of life and function. Furthermore, it is never too late to start HRT/ERT to provide a protective effect on bone density. Women who have had their ovaries removed because of gynecologic disease have a dramatic acceleration of bone density loss if estrogen is not replaced. If they are started on estrogen before they leave the hospital, they rarely lose bone density; if they wait 3 years and then start, they lose some density but then gain most of it back and stop losing it; 6 years later, they have not gained any, but they do stop losing bone density. These data suggest that even many years after menopause occurs or ovaries are removed, bone density can be maintained and protected with HRT/ERT.¹³

Other preventive therapies include calcium and exercise; however, neither one alone nor both together is enough to protect from the rapid bone density loss that may occur after menopause.^{14,15} Bisphosphonates are effective agents for both the prevention and treatment of loss of bone density.^{16,17} Bisphosphonates that are currently available include etidronate (Didronel), alendronate (Fosamax), and risedronate (Actonel). Nasal calcitonin may be adequate for the bone

density loss that occurs in later years.¹⁸ Raloxifene (Evista) is about one third as potent a bone protector as estrogen with respect to bone mineral density,^{19,20} and therapeutic fluoride has not been found to produce bones that are structurally stronger.⁴

Oral health. Oral health may also be linked to menopause. Approximately one third of women older than age 65 years have no teeth because of systemic bone loss in the mandible, particularly after menopause.²¹⁻²³ This oral bone loss contributes significantly to tooth loss, which may turn out to be 1 of the early signs of osteoporosis. Limited data suggest a protective effect of estrogen in tooth retention.²⁴⁻²⁶

Osteoarthritis. Osteoarthritis is the most recent area to be studied. Again, although data are limited, they suggest that a woman may be able to reduce her risk and the consequences of osteoarthritis by taking estrogen over time.²⁷

Cardiovascular disease. Cardiovascular disease is the leading cause of death among women: 1 in 2 will eventually die of heart disease or stroke. Approximately 400,000 American women died of cardiovascular disease in 1999, 100,000 of whom were younger than age 65 years.²⁸ If asked how they will die, however, most women will answer "breast cancer," from which 1 in 25 will die (48,500/year).²⁹

Stroke. Data available on stroke are not nearly as clear as those on cardiovascular disease, probably because the studies did not discriminate adequately between hemorrhagic and thrombotic stroke.³⁰⁻³⁴ Future studies may well demonstrate some benefit of estrogen on certain types of stroke syndrome.

Age-related macular degeneration. Adult-onset or age-related macular degeneration is the leading cause of legal blindness in older women in the United States. A total of 25% to 60% of new cases are diagnosed during the

early stages, when it is usually asymptomatic. No good medical and very limited surgical therapies are available to treat its late stages.³⁵

The pathogenesis of age-related macular degeneration is not known, but it may be related to smoking. A large case-controlled study indicated that women who had taken estrogen had about a 50% reduction in the occurrence of age-related macular degeneration.³⁶ Recent data on cataracts suggest variable degrees of protection when estrogen is taken over long periods of time, resulting in a reduction in incidence.³⁷⁻³⁹ Central retinal vein occlusion may also be reduced with the use of estrogen.⁴⁰

Colon cancer. Colon cancer is the third leading cause of both cancer incidence and cancer deaths in women. The incidence rises at age 40 years and peaks at between 60 and 75 years of age. It is more common in women than in men (although men have more rectal cancer than women, women have more upper colonic malignancy than men). There are an estimated 50,000 new cases each year in the United States and approximately 24,000 deaths.⁴¹ Studies suggest that women who take ERT/HRT have about half the risk of developing colorectal cancer than those who do not.⁴²⁻⁴³

Diabetes mellitus. Diabetes affects about 15.7 million people in the United States, a third of whom have not yet been diagnosed. It is a costly disease, both economically and socially. Diabetes is the leading cause of end-stage renal disease, lower limb amputation, and blindness in younger patients.⁴⁴

The risk of heart disease in diabetic women is increased 5-fold; in essence, diabetes mellitus completely erases the benefit that women in their premenopausal years enjoy over men in the risk of cardiovascular disease.⁴⁵⁻⁴⁸ Women with diabetes who take ERT/HRT in the first few years show no apparent benefits or

increased risks, but long-term therapy may convey protection.⁴⁹

Alzheimer's disease. Alzheimer's disease is estimated to affect 4 million people in the United States and is expected to quadruple in the next 50 years.^{50,51} The rate is 2-fold to 3-fold higher in women, some of which is accounted for by the fact that women live longer than men and some of which seems to be a gender-related predilection.^{50,51} Few women are aware that HRT may protect from Alzheimer's disease; however, delaying admissions to nursing homes by 1 month could easily save \$1.2 billion annually in healthcare costs.⁵² Data also are available demonstrating that HRT may have a beneficial effect in Parkinson's disease.^{53,54}

Deep venous thromboembolism. If 100,000 women between ages 50 and 60 years were treated with estrogen, the attributed additive risk of estrogen to any underlying thromboembolic disease would result in 5 more deaths.^{55,56} However, this risk is modest in comparison with risk of cardiovascular disease or myocardial infarction (MI).

Women and Cardiovascular Disease

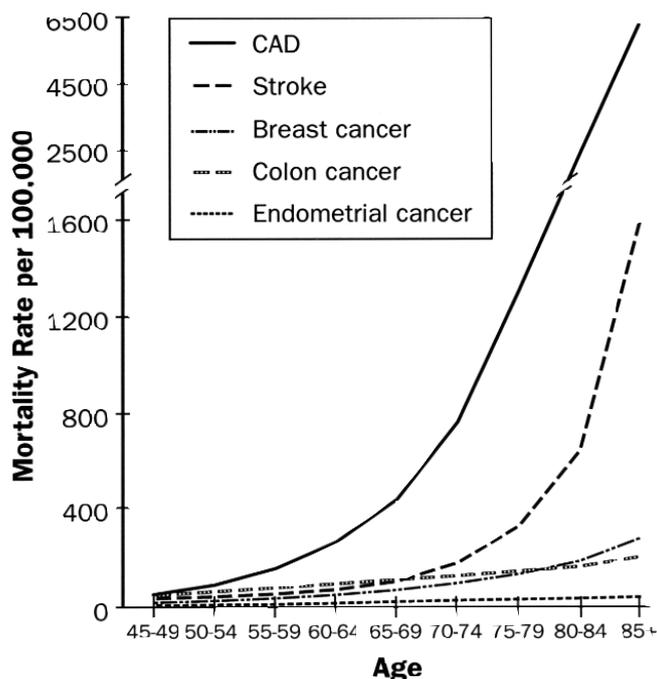
Coronary artery disease is the most frequent cause of death in women age 50 years and older, followed by stroke and carcinomas of the lung, breast, colon, and endometrium (Figure 1).^{29,57,58} The mortality rate for women who have an MI is higher than that for men, as is the recurrence rate of MI postinfarction.²⁸ The morbidity and mortality rates of angioplasty and bypass surgery, 2 of the major advances in treating CAD, are also higher for women.²⁸ These higher rates underscore the importance of not waiting until women have CAD to treat it and the need to prevent its development.

Factors that affect plaque growth in arteries, which may eventually cause MI or stroke, include increased oxidation and uptake of the so-called "bad"

low-density lipoprotein (LDL) cholesterol and increased insulin, among others. The process of atherosclerosis is believed to begin in childhood and becomes anatomically significant after menopause.⁵⁹

A study that examined the effect of estrogen on coronary vasoreactivity found that when women with normal coronary arteries are exposed to the neurotransmitter acetylcholine, endothelium-derived relaxing factor is released, increasing coronary blood flow and vessel diameter.⁶⁰ Adding estrogen results in further increases in coronary blood flow and in vessel diameter. When women with atherosclerosis but without estrogen are exposed to acetylcholine, however, the opposite occurs: their already

Figure 1. Mortality Rates in Women from Heart Disease, Cancers, and Stroke



Source: References 29, 57, 58.

reduced coronary blood flow and vessel diameter size are further compromised. Both are increased when estrogen is introduced. These results indicate important physiologic changes in the coronary arteries of women, particularly in those with early atherosclerotic plaques.⁶⁰

Women who take some form of HRT after menopause have an approximately 50% reduction in cardiovascular mortality.⁶¹ About one third of the benefits are related to plasma lipid-dependent mechanisms; ie, they can be linked to raising high-density lipoprotein (HDL), the "good" cholesterol. Hormones can also lower LDL and lipoprotein little A antigen [Lp(a)] and reduce LDL oxidation, all risk factors for cardiovascular disease. Perhaps more important are some of the plasma lipid-independent mechanisms, including the direct influence of estrogen on the lining of endothelial cells, an increased effect on insulin sensitivity, and on the ability to dilate the coronary vessel and decrease the plaque uptake of LDL cholesterol. As a result, ERT/HRT has a dual benefit in coronary and vascular disease, not only by influencing lipids but by causing direct vascular changes within the coronary vessel.⁵⁹

The National Cholesterol Education Program, which in the past has primarily emphasized lowering cholesterol and LDL to reduce cardiovascular events, is now recommending that HDL also be raised.⁶² This is because a low HDL has been found to be the single most frequent abnormality in patients younger than age 60 years who have had MIs.

A number of observational studies on HRT and the development of cardiovascular diseases have found a reduction in relative risk.⁶³⁻⁷³ An angiographic analysis that followed 3 groups of women for 10 years (eg, those with normal coronary arteries, moderate CAD, and serious CAD) found that those who had used ERT had stable

survival rates. However, those who had not used ERT had a progressive decline in survival rates.^{74,75}

Sullivan et al examined the relationship between ERT and its effect on the lipid profile and anatomic CAD. The trial included 90 consecutive postmenopausal women undergoing elective diagnostic cardiac catheterization over an 8-month or 9-month period to prove the presence and extent of CAD. A lipid profile was obtained on each patient. Excluded were those who had a recent MI, had unstable angina, were on a cholesterol-lowering agent, or had undergone previous coronary bypass surgery. Total cholesterol values were similar in those who had taken estrogen at some time versus those who had never taken estrogen; LDL was slightly lower in the former group.⁷⁴

Further analyses determined that the lack of estrogen use was the most powerful independent variable relating to the presence of CAD (in addition to asking postmenopausal women about chest pain). In the study, women who underwent coronary angiography for suspected CAD and had never taken estrogen had approximately an 84% incidence of disease during catheterization; of those who had been on estrogen, only 17% had anatomic disease. Thus, estrogen use at some time resulted in an 87% reduction in angiographic CAD. Women who had taken estrogen at any time had a significantly higher HDL and a lower total cholesterol to HDL ratio (used as an index for future cardiovascular events), with lack of estrogen use being the best predictor of anatomic CAD at cardiac catheterization.

One of the studies that has received a great deal of attention over the past 2 years is the Heart and Estrogen/progestin Replacement Study (HERS).⁷⁶ This randomized, double-blind, placebo-controlled trial was designed to compare the efficacy and safety of HRT (0.625 mg conjugated equine estrogens [CEEs]

plus 2.5 mg medroxyprogesterone acetate [MPA]) in the protection of recurrent CAD in 2763 women with documented disease.

The women in the HERS trial were 67 ± 7 years of age and a number of them had additional risk factors, including a history of diabetes (18%), smoking (13%), or being overweight (55%). Many were taking concomitant medications: aspirin (78%), β -blockers (32%), lipid-lowering agents (45%), diuretics (28%), angiotensin-converting enzyme (ACE) inhibitors (17%), and/or calcium channel blockers (55%).

The results were surprising: during the first year of the trial, women on HRT had a slightly increased incidence of a second coronary event compared with women taking placebo. By the second year, however, those who remained on HRT had a consistent and significant reduction in cardiovascular events compared with the placebo group through years 3, 4, and 5 of the study. This has resulted in recommendations that physicians carefully evaluate HRT for women with established coronary heart disease. However, the HERS trial results were not inconsistent with observational studies suggesting the benefit of HRT in primary prevention of cardiovascular disease.

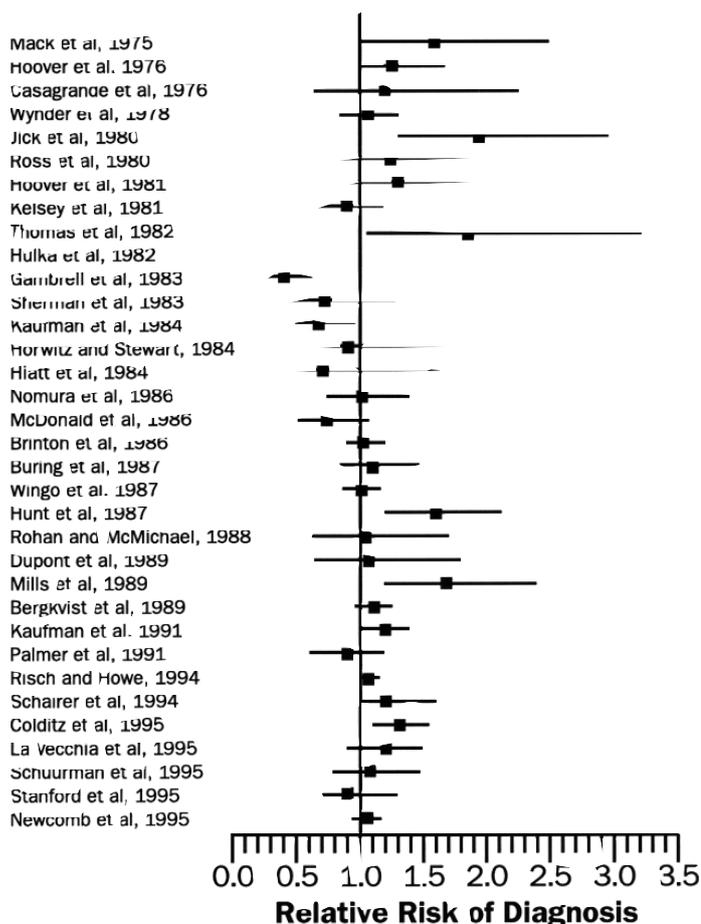
Given the impact of estrogen deprivation—an increase in coronary artery atherosclerosis, coronary artery obstruction, and cardiovascular events—ERT/HRT remains a viable option for reducing cardiovascular risk in postmenopausal women. Statins,⁷⁷ antioxidants,⁷⁸⁻⁸⁰ and aspirin⁸¹ also all have a positive effect on cardiovascular risk.

Managing Patient Concerns

Breast Cancer. A 1990 Gallup survey asking women why they refuse HRT and physicians why they do not prescribe HRT identified an increased risk of breast cancer as the number 1 concern for each. A decade later, this remains the primary concern among both women and physicians.

Results of studies to date have continued to fuel this controversy. However, most of these studies have concluded that the relative risk of developing breast cancer with the use of HRT is 1.0—in other words, no greater than the risk in the general population (Figure 2). Retrospective studies of breast cancer mortality among healthy women who used ERT/HRT found they had a lower risk of dying.⁸² This may be the result of 1 of several reasons: women who take hormones receive better healthcare; they may get mammograms earlier, allowing for earlier detection and

Figure 2. Relative Risk of Breast Cancer with ERT/HRT



Source: Reference 4.

cure; or the hormones themselves may be protective, producing a less aggressive tumor.

A family history of premenopausal breast cancer in women who took hormones and eventually developed the disease has been found to be an independent predictor of favorable prognosis. In 95 women between the ages of 25 to 45 years with a family history of premenopausal breast cancer, those who took HRT had a greater chance of having negative lymph nodes than those who did not take HRT (48% versus 32%); similarly, they were more likely to be alive at 5 years (92% versus 70%) and 10 years (87% versus 54%). Multivariate analysis found these high-risk women had a 6 times greater chance of surviving breast cancer if they took hormones.⁸³

Another recent study, the first to look at tumor characteristics, found that women who were on ERT when they developed breast cancer were diagnosed with a less aggressive tumor type⁸⁴; this has also been the case in endometrial cancer.^{85,86}

Use of ERT/HRT after a diagnosis of breast cancer currently is contraindicated by the US Food and Drug Administration. However, 3 small retrospective (observational) studies have found that women who took hormones had no greater incidence of breast cancer recurrence than the general breast cancer population.⁸⁷⁻⁸⁹ In the meantime, they have derived the benefits of HRT for osteoporosis, cardiovascular disease, and overall quality of life. Women with recurrence of breast cancer who have taken hormones also do not appear to die earlier of their breast cancer.^{90,91}

In counseling women about the risks of breast cancer with ERT/HRT, physicians should note that there is no clear clinical evidence to suggest exogenous estrogen induces carcinoma. Women at high risk of breast cancer—those with a genetic predisposition or previous atypical hyperplasia on breast biopsy—who want to

consider hormone use should be provided with information about risks and benefits to enable them to make a decision. In the general population, hormones are beneficial; if breast cancer is detected, the survival period has been shown to be statistically longer. Patient education can also help alleviate misconceptions and fears about hormones and breast cancer risk. Often, a woman will stop taking HRT based on what she hears from family, friends, or even relative strangers; the physician is often the last to know.

Selective estrogen receptor modulators (SERMs). The recent approval of SERMs for clinical use has focused attention on the different effects of estrogen on body target organs. For example, the SERM tamoxifen has 3 indications: as adjuvant therapy for women with early breast cancer; for primary prevention of breast cancer in healthy high-risk women; and as first-line treatment for estrogen receptor-positive metastatic breast cancer.⁹² Raloxifene is indicated for the prevention of osteoporosis, and toremifene is a first-line treatment for estrogen receptor-positive metastatic breast cancer.²⁰

In considering the use of SERMs, a woman's quality-of-life issues should be reviewed, including hot flashes, nausea, vomiting, vaginal dryness, vaginal bleeding, menstrual irregularities, mental depression, and leg cramps. Neither tamoxifen nor raloxifene has an affect on Alzheimer's disease.

Antioxidants and alternative therapies. Studies have shown that the individual components of CEEs exhibit dramatically different abilities to inhibit LDL oxidation. Bhavnani et al⁹³ compared several estrogens to 17 β -estradiol to determine their ability to delay oxidation lag time. Δ -^{8,9}-DHES was found to be a potent LDL antioxidant when compared with the cholesterol-lowering drug probucol, with quercetin and t-resveratrol (the components in red wine), with vitamin E (an

endogenous antioxidant), and many of the other estrogens in CEE.

Currently, little data exist on herbal remedies such as soy protein. One role currently being investigated for soy phytoestrogens in postmenopausal HRT is focusing on their antiestrogen effects at the level of the breast and the uterus; these effects suggest that, when combined with low-dose estradiol, the need for a progestin may be obviated.⁹⁴ The amount of soy necessary to possibly reduce the incidence of breast cancer while also relieving hot flashes is not yet known.

Central Nervous System Benefits of Managing Menopause

A growing body of evidence suggests estrogen's beneficial effects on the central nervous system (CNS) should be added to the risk-benefit equation when considering the use of HRT in postmenopausal women.

One of the proposed benefits of estrogen is increased central processing speed within the CNS. Studies of postural stability in older and younger women have found that older women who took estrogen performed much like younger women on tests of sway velocity, whereas older women who had not taken estrogen had much worse balance.⁹⁵⁻⁹⁷ When younger women fall, they react by putting their hands in front of them, which breaks the fall and may result in a wrist fracture, but older women with slower central processing speed may not put their hands out in time, increasing the likelihood of a hip or skull fracture. It is hypothesized that estrogen replacement may increase central processing speed in older women, allowing them time to re-establish balance and avoid a fall or to break a fall with their arms.⁹⁷

Research suggests a relationship between estrogen and a number of neurotransmitter systems within the brain.⁹⁸⁻¹⁰⁰ These include the noradren-

ergic and serotonergic systems, both of which are implicated in mood disorders and depression; the cholinergic system, implicated in learning, memory, and Alzheimer's disease; and the dopaminergic system, implicated in movement disorders such as

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Parkinson's disease and peripherally related to mood disorders. Studies demonstrate beneficial effects on cognition for normal postmenopausal women¹⁰¹ as well as for women with Alzheimer's¹⁰² or Parkinson's disease.¹⁰³ Estrogen also has been associated with a delay in onset of both Alzheimer's disease¹⁰² and Parkinson's disease.⁵⁴

Overall, estrogen has an antidepressant effect on mild states of dysphoria.¹⁰⁴ Specifically, it increases serotonin synthesis and postsynaptic responsivity, making each receptor more sensitive to available serotonin molecules. It also increases norepinephrine turnover and has a mixed effect on dopamine and endorphins. For women with a prior history of depression, HRT around the time of menopause may decrease vulnerability to subsequent periods of depression. Estrogen may also be a useful adjunct to conventional therapy that may either shorten time to response or time to treatment resistance. In a study of women taking fluoxetine (Prozac), the best responders turned out to be individuals who were also taking HRT.¹⁰⁵ The exact mechanisms of this response are not yet known.

One study found that young women who had both ovaries removed but

who subsequently received estrogen had significantly improved cognitive scores from baseline.³ In addition to learning and memory, other domains of cognition that have also recently been demonstrated to be affected by estrogen include language, abstract reasoning, and visual spatial perception.

Alzheimer's disease. The latency period between initiating factors and clinical symptoms of Alzheimer's disease is estimated to be 15 to 20 years. Initiating factors can be genetic, such as Apolipoprotein E (APOE), an inherited cholesterol-modulating gene, or environmental, such as exposure to chronic oxidative stress and inflammation.¹⁰⁶⁻¹⁰⁸

When a woman has a neurodegenerative disease such as Alzheimer's, there is evidence of oxidative stress, which contributes to the development of diffuse plaques in the brain. Oxidative stress itself can cause neuronal death and indirectly contributes to plaque formation. The development of diffuse plaques in the brain is not necessarily problematic; autopsy results have shown diffuse plaques in patients who were cognitively normal. However, when plaques aggregate and collect β -amyloid, they are termed neuritic plaques, which are toxic. Intraneuronal tangles develop simultaneously in certain parts of the brain, resulting in neuronal damage and synaptic loss. If diffuse plaques can be kept from developing or turning into neuritic plaques, the entire process can be shifted in time. If the onset of Alzheimer's disease can be delayed for 5 years by early intervention, its prevalence can be decreased by about 50% by the middle of the 21st century.

A meta-analysis of 10 studies found a 29% reduction in the risk of Alzheimer's disease if a woman took HRT when she was postmenopausal, and the Leisure World Cohort Study found a dose-response effect of estrogens: The longer a woman took estrogen, the greater protection it conferred.¹⁰⁹ Estrogen is believed to sig-

nificantly limit oxidative damage and has a number of biological mechanisms that assist in limiting the development of diffuse plaques.^{110,111} Estrogen also inhibits APOE levels in plasma.

Estrogen has a significant impact on the growth of cholinergic neurons, which produce the neurotransmitter acetylcholine, known to be reduced in Alzheimer's disease. It also works in synergy with tacrine (the first compound approved to treat Alzheimer's disease),¹¹² which also prevents the breakdown of acetylcholine. This mechanism of action is not yet understood.

Parkinson's disease. Few studies have been conducted of the effect of estrogen on Parkinson's disease. However, some similar patterns are emerging in the literature that suggest estrogen limits oxidative processes within neurons relevant to Parkinson's disease, thus delaying disease onset.

Several small studies suggest estrogen has a direct beneficial effect on the pharmacokinetics of levodopa, including a reduced levodopa threshold, resulting in a lower levodopa dosage for patients.¹¹³⁻¹¹⁶ It should be noted that in young women, estrogen has been associated with an infrequently occurring levodopa-related dyskinesia.¹¹⁷

In one study of Parkinson's disease, the relationship of symptom severity and estrogen use was investigated.⁵⁴ Estrogen was associated with much lower (ie, better) scores on the Unified Parkinson's Disease Rating Scale throughout the course of the study. None of the women started levodopa therapy before or during the study period. The results indicated that estrogen therapy limited Parkinsonian symptoms throughout the course of the disease before exposure to levodopa. One study has demonstrated a later age of onset of Parkinson's disease for women who took estrogen replacement after menopause.⁵³

About 40% of patients with Parkinson's disease develop dementia. Results of a clinical study evaluating women with Parkinson's disease using a battery of cognitive tests found those with the disease had a similar ability to learn new verbal material regardless of ERT use but that use was associated with better retention of the material learned.¹⁰³

In summary, the limited data available indicate that estrogen may reduce the risk and age of onset of Parkinson's disease, disease severity, and disease-related cognitive dysfunction and may improve the efficacy of medication for the disease. Although these data are preliminary, there is sufficient suggestion of beneficial effects to warrant further study.

Individual risk profile. At some point, a woman will ask: "Should I take estrogen?" As important as it is to have her understand how estrogen works on multiple systems, it is more important to look at her individual risk profile. Questions can include: "Who in your family has high blood pressure?" "Who in your family had a heart attack?" "Who in your family got shorter and smaller as they aged?" or "Who had memory loss?" This will result in a profile that is meaningful to a woman and provide a context in which information about ERT/HRT can be presented in relation to her own situation. It also provides an opportunity to make diagnoses relevant for her risk profile, which previously may not have been done. After developing a personal risk profile, other peripheral information can be added that may not be as relevant to her situation, such as the risk of colon cancer. Whatever the approach, it should initially get a woman's attention, then relate information pertinent to her situation and finally include a review of additional information.

**Management of Menopause:
Opportunities for Intervention**

When discussing the benefits of

HRT on various target tissues with women, it is important to remember that women are more than simply estrogen receptors: They are emotional, physical, and spiritual beings, the

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latter of which includes belief systems. Women enter physician offices with these belief systems, which drive what they choose to do. For example, if women believe they are going to die of heart disease and not of breast cancer, this will influence the way they think about HRT and aging. Or, "baby boomer" women who may have grown up questioning authority may be skeptical about ERT/HRT messages, especially if they came of age in the era of high-dose estrogen oral contraceptives and experienced symptoms of bloating or weight gain. Cross-cultural issues may also influence decisions: Asian women may believe they are not at risk for breast cancer; Hispanic women may hold a similar belief about another disease.

Counseling women for HRT use should occur on 2 levels: 1 that discusses relief of early symptoms of menopause, such as hot flushes, irritability, and agitation, and another that discusses late manifestations, such as the risk of developing cardiovascular disease or osteoporosis. This is important, because 20% of women who take ERT/HRT for the first time stop within 9 months once their early symptoms are under control. Ten percent will use it only intermittently; another 20% to 30% will "yes their physicians to death," walk out the

door and never fill the prescription, or cannot afford to have it filled.

It is also important for physicians to be willing to discuss any fears surrounding HRT. Questions to ask include, "What do you know about HRT?" or "What do you think about HRT?" The correct use of HRT, along with available options and anticipated side effects, can form the basis of a discussion, as can asking about any natural remedies a woman might be using. Bloating, weight gain, constipation, breast tenderness, and headaches should be addressed, because women will often stop ERT/HRT for any of these reasons. A woman may also stop when she no longer has any menopausal symptoms and cannot see a reason to take it. Besides fear of an increased risk of breast cancer, a woman also may not take ERT/HRT because she senses an ambivalence from her physician.

Before determining that a woman will not begin or continue to take ERT/HRT, physicians should inform her of its myriad benefits, encourage her to start or stay on therapy, and/or offer a different dosing regimen or method of delivery (oral, transdermal, vaginal rings, or intrauterine devices) better suited to her needs. Sexuality often is not discussed, but vaginal dryness, pain on penetration with intercourse, risk of sexually transmitted diseases (especially if a woman has been recently widowed or divorced), and decreased libido, arousal, clitoral sensitivity, and orgasm intensity and frequency are all appropriate topics for discussion with postmenopausal women.

Women now in their 40s, 50s, and 60s are at the beginning of a new era in aging. The challenge for physicians is to be accessible to women and listen to them, to answer their questions, address their fears, offer therapeutic options, advise them of the importance of moderation in diet and alcohol consumption, increased exercise, and quitting smoking, and to respect their

decisions. The emphasis should not be on whether a woman is taking a prescription the way she has been instructed but on how physicians can help her be successful in living a long and healthy life.

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