Controversial issues in climacteric medicine III
Hormone replacement therapy in climacteric and aging brain

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Position Paper

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INTRODUCTORY REMARKS

This paper is based on the consensus established by the group of experts participating in the Third Workshop in the 'Controversial Issues in Climacteric Medicine' series of Workshops of the International Menopause Society (IMS), dedicated to the theme of 'Hormone replacement therapy in climacteric and aging brain'.

This meeting was organized by the IMS in order to review available literature and unpublished work on the complex subject of the effects of the menopause and of hormone therapies on the nervous system.

The aim of this meeting was to suggest state-of-the-art guidelines for research and practice on these themes. This Position Paper arises from the presentations and from the ample discussion held during the sessions. It is neither perfect nor complete in its representation of all aspects of the subject, or even of the 'give and take' of the Workshop.

BASIC SCIENCE

CNS development and structure are regulated by steroid hormones

Sex steroid hormones play fundamental roles in the development and function of the central nervous system. Marked differences are found in the structure and function of the brains of male and female animals and humans. These differences highlight the importance of sex steroids in the development and regulation of the central nervous system.

Indeed, in humans and in rats, several areas of the brain show gender dimorphism, as indicated by differences in structure (such as different numbers of cells in specific areas). The different organization of areas of the brain in males and females appears to be largely dependent on the action of sex steroid hormones, and the differential expression of steroid receptors and of aromatase in sexually dimorphic nuclei supports this hypothesis. This is also suggested by evidence that the levels of circulating and locally produced steroids control the structure and activity of sexually dimorphic nuclei. This finding also implies that exogenous sex steroids could cause differences in the structure/function of specific brain areas, with measurable clinical effects.

Although abundant morphological and functional evidence exists for sex differences in brain development, much less is known regarding the underlying developmental mechanisms that direct these differences. It is clear that gender-associated differences are highly selective, such that one area of the brain may be activated by a steroid hormone, while another area is unaffected or exhibits the opposite response.

While these sex-specific differences exist in animals, these observations may not be generalized to include humans, as significant variations exist between animal species and humans in the structure/function of different brain areas. However, since there is a developmental program, the timing as well as the agent and its amount are important in the outcome. Evidence has accumulated that, since neurons are limited in their proliferative life and there is considerable programmed cell death after birth, the effect of steroids appears to involve regulation of neural cell kinetics and apoptosis. In any case, sexual dimorphism is also present in other cellular compartments such as the astroglia, and the sex steroid-related developmental differences seen in both animals and humans are both real and complex.

The central nervous system (CNS) exhibits the potential for dynamic restructuring throughout the life span. The plasticity of the brain is most apparent during early development in formation of the nervous system, but it continues throughout puberty and reproduction. Estrogen-induced synaptic plasticity is clearly seen during puberty and seasonal changes, as well as during the ovarian cycle. Once established, neural networks are highly responsive to both endogenous and environmental factors that remodel neural circuitry. This has been best studied and proven in the hypothalamus, hippocampus and cortex; these areas have been shown to respond to estrogen deficiency and replacement in women. Steroid hormones are major factors inducing remodelling. Indeed, the content and distribution of steroid receptors in the brain (estrogen receptor (ER), androgen receptor (AR)) change throughout the life span, including during the process of aging. Additionally, specific modifications in steroid receptor distribution can be found in pathological conditions such as Alzheimer's disease, which accompany and potentially play a role in the dysfunction of the areas characterized by degenerative processes.

The CNS is both a source and a target of steroid hormones

The CNS is both a source and a target of sex steroids and of their metabolites.

Neurons and glial cells possess enzymes necessary for progesterone, testosterone and estradiol metabolism (aromatase, 5α-reductase (mainly in neurons), 3α-hydroxysteroid dehydrogenase (mainly in type 1 astrocytes)). The activities of these steroid-metabolizing enzymes are strongly influenced by the differentiation/maturation process of the precursor stem cells into terminally differentiated CNS cells. Neurons and glial cells co-ordinately metabolize steroid hormones, thus forming a functional unit; however, they may also react independently to different steroids.

While steroid-metabolizing enzymes render the CNS able to modify circulating steroids, the CNS is also able to synthesize steroids from cholesterol, leading to the production of a series of potent steroidal compounds. These brain-specific hormones have been named 'neurosteroids', and have been found to exert important regulatory actions on neurons and glial cells.

During reproductive life, circulating sex steroids play a substantial role, whereas, in post-reproductive life, local formation and metabolism of steroids assume a greater importance. To this extent, the content and distribution of steroid-metabolizing enzymes may be of particular significance in preserving the endocrine function and responsiveness of the brain. Indeed, data obtained in animals suggest that aromatase (which converts androgens to estrogens in neurons and, apparently under stress, in glial cells) is important for the determination of sexual behavior, cognition, memory and mood. In addition, prominent degenerative processes in the neural cell can be seen in aromatase-deficient mice, therefore suggesting that local conversion of androgens to estrogens may have a primary role in preserving neuron integrity.

There is also an enlarging body of evidence of the diverse neuroprotective effects of estrogen. This is a very vital and important area of study. Evidence indicates that estrogen prevents CNS damage and dystrophy but is not involved in repair. This has implications for strategies that furnish prevention and not treatment. Similar actions are seen in other systems such as blood vessels. This raises many unanswered questions regarding both the length of time needed for establishing prevention and how long after the menopause such prevention can be accomplished.

Glial cells and aging

Organ-specific changes occur during aging in multiple systems (cardiovascular, endocrine, immune and nervous systems) and interact with brain senescence. The reverse is also true, as neuronal and glial functions are affected by endocrine status, and significant changes occur with aging in steroid receptor distribution and expression throughout the brain.

Glial cells are affected by aging, and specific changes may be observed. For instance, modifications of extrasynaptic 'volume' transmission can be seen in aged brains, owing to the loss of extracellular matrix and to narrower intercellular clefts. Progressive loss of the orientation and number of glial processes (anisotropy) and replacement of neurons by hypertrophy and proliferation of glial processes are also seen with aging (gliosis). Deposition of macromolecules (e.g. amyloid) can be seen with aging, as well, and is a typical feature of pathological conditions such as Alzheimer's disease.

Structural and functional modifications contribute to the reduction of diffusion of neuroactive substances in the extracellular space, therefore leading to the progressive decline of synaptic and extrasynaptic transmission and of synaptic plasticity, ultimately helping to explain reduced brain performance.

Immunocyte–sex hormone interactions (the immune system–brain barrier)

The immune system exerts a series of important actions in the brain. First, it maintains homeostasis, the silent cleaning and refurbishing of the brain. The brain is constantly assaulted by free radicals, metabolic waste, trauma, infectious disease, etc. While the immune response is fundamental to the maintenance of CNS homeostasis, if excessive or not regulated, immune reactions can damage brain cells, even destroying neural processes and cell bodies to avoid excessive immune responses. There are 'speed bumps' or immune checkpoint proteins that must be negotiated before the immune reaction can be enacted. This avoids unnecessary destruction.

Estrogens may modulate cellular and humoral immune responses. Particularly, estrogen regulation of the brain immune system maintains the immune response under control. This regulation of checkpoint proteins, such as the Fas–Fas ligand system as well as the CD40–CD40 ligand system, is strengthened by estrogen. The result is a healthier brain which is serviceable for a longer period.

Within the various CNS cell types, including astroglia, estrogens have been shown to regulate

microglial cells at several levels, specifically modulating microglial expression of cytokines and growth factors.

Given the relevance of the actions of estrogens on immune system–brain interactions, it may be expected that, in the absence of estrogen, less restricted immune responses may hasten clinical brain disorders.

Neurosteroids and GABA-A signalling

Neurosteroids are steroids synthesized in the CNS from blood-borne precursors as well as *de novo* from cholesterol.

The brain metabolism of progesterone determines the brain content of active neurosteroids such as allopregnanolone, a γ-aminobutyric acid-A (GABA-A) receptor positive allosteric modulator with a physiological role in modulating mood, emotional states and affectivity.

Fluctuating concentrations of central neurosteroids modulate GABA-A receptor function (via rapid, non-genomic mechanisms involving direct interaction with surface receptors) as well as gene expression (through GABA-A receptor-dependent genomic, i.e. transcriptional, mechanisms). Changes in GABA-A receptor gene expression, in turn, may lead to the synthesis of novel receptor subtypes endowed with different physiological as well as pharmacological sensitivities.

Fluctuating concentrations of central neurosteroids modulate GABA-A receptor gene expression (through genomic, i.e. transcriptional, induction) as well as function (via rapid, non-genomic mechanisms).

Brain levels of allopregnanolone increase during acute stress, in pregnancy and with antidepressant and anxiogenic drugs; on the other hand, they decrease during chronic stress, parturition and depression.

It is of interest that several GABA-A receptor agonists, such as benzodiazepines, barbiturates, alcohol and the progesterone metabolite allopregnanolone, seem to have biphasic effects on CNS-related symptoms in both humans and animals. In high doses, one type of effect (inhibition) is seen, while low doses result in the opposite effect (disinhibition). Allopregnanolone has anxiolytic, sedative and antiepileptic effects; some of these are seen in both humans and animals, others only in animals. Low doses of allopregnanolone and alcohol increase aggression in rats, while higher doses of allopregnanolone and/or alcohol decrease aggressive behavior.

Neurobiology of steroids and steroid receptors in the CNS

Estrogens

Estrogens act on neuronal and glial cells via both direct and indirect mechanisms. During brain development as well as in the fully differentiated CNS, estrogen promotes new neural circuit formation in selected regions of the brain, most notably those brain regions associated with cognitive function, the hippocampus and cerebral cortex.

Importantly, estrogen can also increase cerebral blood flow, thus regulating vessel tone, and therefore improving brain cell nutrition and function.

Multiple mechanisms of estrogen action have been demonstrated. These include potentiation of acetylcholine synthesis and release, potentiation of excitatory signalling, enhancement of long-term potentiation, and augmentation of the number of dendritic spines. Each of these responses is thought to contribute to estrogen-modulated memory function.

Intracellular mechanisms that underlie estrogen-inducible cognitive function and neuroprotection against degenerative disease include regulation of intracellular calcium concentration, activation of signalling cascades associated with memory function and neuroprotection, including the mitogen-activated protein kinase (MAPK), phosphatidylinositol-3 kinase (PI3K)/Akt and cyclic AMP-responsive element binding protein (CREB) transcription factor regulation of gene expression. Genes known to be regulated by estrogen through a CREB-dependent mechanism include the antiapoptotic proteins Bcl-2 and Bcl-X.

In addition to MAPK activation, estrogens can potentiate insulin-like growth factor-I (IGF-I) receptor signalling in the brain, stimulating its recruitment of the PI3K/Akt pathway. By binding to ERα, estradiol may also signal directly to PI3K and Akt and has been shown in other cells to synergize with IGF-1. In both cases, estrogen would lead to enhanced Bad phosphorylation, and therefore to escape from programmed cell death and to activation of cell survival mechanisms.

Estrogens can also exert antioxidant effects to inhibit peroxidation, thereby protecting neurons against oxidative stress. An additional brain-sparing action of estrogen may rely on the recently identified inhibition of expression of the receptor for cytotoxic advanced glycation end-products (AGEs).

In several models of Alzheimer's disease, estrogen treatment reduced β-amyloid deposition. These findings, coupled with the neuroprotective actions of estrogen, support the emerging clinical data which indicate that estrogen replacement therapy has the potential to delay the onset or reduce the risk of neurodegenerative diseases such as Alzheimer's disease.

In conclusion, the vast majority of the actions of estrogens are thought to be beneficial, and estrogens may therefore be considered as neuroprotective steroids.

Progesterone

While a certain amount of evidence has been collected on the biological basis of the effects of estrogens on brain cells, less is known about how progesterone, and even less how the different synthetic progestins in therapeutic use, may regulate neurons and glial cells.

However, increasing evidence indicates that progesterone has potent effects on the central as well as the peripheral nervous system, where it stimulates myelination and re-myelination. These actions of progesterone are also shared by the reduced progesterone metabolites, which stimulate the growth of glial precursors and myelination by acting on progesterone receptors (therefore activating traditional nuclear signalling pathways), as well by recruiting GABA-A receptors (and by this means exerting rapid nongenomic modulations of ion concentrations in the cells, leading to cell phenotype changes). Reduced progesterone metabolites have also been shown to stimulate the proliferation of glial precursor cells.

Progesterone shares with estrogens the ability to activate MAPK cascades, so that it may also induce cell proliferation and survival through similar mechanisms.

Recent evidence indicates that synthetic progestins do not share with progesterone the same effects in the brain. *In vitro* model studies indicate that progesterone is neuroprotective against toxic insults associated with Alzheimer's disease, while medroxyprogesterone acetate is not. Moreover, whereas progesterone synergizes with estrogen to enhance neuroprotection, medroxyprogesterone acetate may not share, or may even oppose, the same action.

The effects of some of the reduced metabolites of progesterone may be mediated by specific receptors, which have recently been identified. These include 25-Dx, which is proposed to be membrane-associated, and microtubule-associated protein 2.

Supporting the *in vitro* data, pregnenolone concentration in the rat brain correlates with spatial memory. Moreover, progesterone and progesterone metabolite concentrations are decreased in Alzheimer's disease patients, supporting the view that these steroids may have neuroprotective effects.

CLINICAL ASPECTS AND TREATMENT

Hot flushes

Hot flushes are one of the more common and earlier symptoms of the climacteric. They are characteristic, sudden sensations of intense heat with sweating and flushing.

Hot flushes appear to be triggered by body temperature elevations exceeding the sweating threshold. Postmenopausal women experiencing hot flushes appear to have a reduced sweating threshold, with a narrowing of the so-called thermoneutral zone. In these women, even small temperature elevations in the body core trigger hot flushes.

Hot flushes are associated with endocrine changes. It is most likely that the decline in estradiol causes increased norepinephrine production in the brain, favoring the generation of hot flushes. The involvement of other neurotransmitters (dopamine, serotonin) and neuromodulators (opioids) cannot be excluded.

Hot flushes typically disappear within 1–5 years in the vast majority of postmenopausal women; this implies some compensatory change in neurotransmitter systems. However, the rapid disappearance of hot flushes does not imply protection from the long-term effects of the menopause on the central nervous system.

Sleep disturbance

Sleep disturbance is a well-documented subjective complaint associated with the menopause, especially during the perimenopause.

When sleep disturbance associated with the menopause is evaluated objectively in the sleep laboratory, however, the association between sleep disturbance and menopause is less clear. One reason is the lack of polysomnographic studies designed specifically to assess this transition. It is, however, well documented that objective sleep disturbance is observed in women who are currently experiencing hot flushes and that hormone replacement therapy (HRT) will reduce this sleep disturbance. Another reason that objective

polysomnographic evaluation of the association between menopause and sleep disturbance is unclear may be the confounding effects of aging and gender on sleep.

In general, sleep quantity and quality decrease with age, and women tend to sleep better than men across all ages (in terms of both quantity and quality). In contrast, women are more likely than men to complain of sleep disturbances including chronic insomnia. Depression, especially dysthymic depression, is strongly associated with chronic insomnia, and women are also more likely to report depression than men. Thus, reports of sleep disruption associated with the menopause could be a direct result of dramatic changes in the hormonal milieu associated with the menopause, or these reports could be associated with other hormonally influenced processes, such as mood changes. Further studies specifically designed to address this question are needed.

Currently available data suggest that estrogens exert sleep-enhancing effects, while progesterone, in the doses employed in HRT, may not.

In contrast to sleep disturbance, women have a reduced risk of sleep apnea compared with men. The menopause is a strong risk factor for sleep apnea. Age is a confounding factor, as the prevalence of sleep apnea increases with age, up to at least the sixth decade in men and the seventh decade in women. In postmenopausal women who use HRT, the risk of sleep apnea appears to remain at the low premenopausal level, in spite of increased age.

The major risk associated with sleep apnea is hypertension and other cardiovascular events, and women with sleep apnea appear to have the same risk of hypertension as that of men with sleep apnea. Thus, postmenopausal women who use HRT appear to be at reduced risk of sleep apnea, and thus at reduced risk of hypertension and associated cardiovascular events due to sleep apnea.

Headache

Headache is more common in females than in males (females : males, 2–3 : 1). Migraine is closely related to sex hormone levels throughout life. Indeed, the onset of migraine attacks often follows the menarche, and many women experience migraine attacks during periods of sudden estrogen change (ovulatory phase, menstrual cycle, surgical menopause). Conversely, conditions of stable estrogen level (pregnancy, spontaneous menopause) can act as migraine stabilizers.

While the severity of migraine tends generally to improve after the menopause, other types of headache, such as tension-type headache, may worsen.

It has been suggested that migraine can result from a condition of hypersensitivity to physiological hormone fluctuations.

In these patients continuous administration of estrogens and progestogens may be better than sequential administration. To this extent, any route of administration of estrogens leading to more stable plasma levels (e.g. transdermal) may be more favorable in women affected by migraine.

Affective disorders

The prevalence of major depression is two-fold higher in women across all age groups (with only a slight preponderance in women for minor depression). Women with depression experience greater suffering and impairment of daily activities, together with as introverted attitude towards depressive symptoms, which may extend their disease.

There may be a slight increase in the prevalence of major depression at age 45–54 which can be interpreted as the age range of climacteric transition. However, the same increase is also noted in men. There is no increase or decrease in the 12-month prevalence of major depression during the menopause, and there is no apparent association between menopausal status and new onset of major depression.

Estrogen therapy has not been shown to be an efficacious sole treatment of depression in postmenopausal women. However, estrogen administration has been reported to be efficacious as an antidepressant only in depressed women during the climacteric transition. Despite several *post hoc* reports and suggestions that estrogen may be an effective adjunct to antidepressants in non-responder women, this has not yet been confirmed.

The initiation of hormone replacement may cause irritability and other dysphoric moods in some hypersensitive women, particularly during the progestin phase of treatment. The effects of estrogens and estrogen–progestin combinations on mood and behavior may vary according to the actual compounds and host characteristics. Changing the type or dosage of progestin used may provide some clinical benefit in these women. The effects of different progestins on mood warrant and require further investigation.

Women with a history of premenstrual syndrome may be especially sensitive to hormone supplementation. In these women, transdermal estrogen administration in association with an intrauterine device releasing a progestin may possibly be an alternative, to avoid the undesirable effects of systemic progestins.

Androgen deficiency and female sexuality: Δ^5-androgens

The adrenal production of Δ^5-androgens, dehydroepiandrosterone (DHEA) and its sulfate ester dehydroepiandrosterone sulfate (DHEAS), declines linearly with age starting from the third decade of life, independent of the menopausal transition, reaching 20% or less of maximum plasma concentrations after 70 years of age. In particular, DHEAS, the most abundant circulating androgen, shows a decrease more pronounced and precocious in women than in men. Cortisol levels, on the other hand, are relatively unchanged throughout life.

Much evidence from the literature has indicated that DHEA administration is able to improve the quality of life in elderly subjects. On the other hand, HRT further reduces circulating Δ^5-androgen levels in postmenopausal women. An endocrine and neuroendocrine impact of DHEA administration in postmenopausal women has recently been examined. DHEA oral supplementation (25–50 mg/day for 6–12 months) in early- and late-postmenopausal women restored levels of Δ^5-androgens, Δ^4-androgens, estrogens (estrone, estradiol), progesterone and 17α-hydroxyprogesterone, and allopregnanolone, as well as growth hormone and IGF-I, similar to those observed in fertile women, while cortisol and gonadotropin levels progressively decreased. DHEA therapy was also able to determine an estrogen-like restoration of basal and stimulated levels of β-endorphin, indicating a modulation of neuroendocrine function.

In addition, a positive effect on Kupperman score, with no changes of endometrial thickness, suggests that DHEA administration in the postmenopause may be considered a possible practical replacement treatment.

Androgen deficiency and female sexuality: Δ^4-androgens

Sexual dysfunction is more frequent in women than in men. Sex steroids act upon the CNS and genitalia. In women, androgens increase libido, sexual fantasies and motivation. The action of estrogens in promoting vaginal lubrication is related to their action on sexuality.

Natural menopause is not related to an immediate decrease in serum testosterone, but surgical menopause produces an abrupt decrease in testosterone owing to ovarian ablation. HRT may further decrease bioavailable testosterone by increasing sex hormone binding globulin (SHBG) concentration. Administration of combined estrogen and testosterone or testosterone alone has beneficial effects on sexual function.

There are no defined cut-off levels for testosterone in postmenopausal women, and the diagnosis of androgen deficiency syndrome should therefore be clinical. At the same time, no guidelines for androgen replacement in postmenopausal women exist currently (that is to say, pharmacological preparations specifically tailored for androgen replacement in postmenopausal women).

Compounds with androgenic activity, such as tibolone, have been shown to improve vaginal trophism, sexual response and sexual well-being in postmenopausal women, and may therefore be considered for hormone replacement therapy in women with clinical features of androgen deficiency.

In a phase II double-blind, placebo-controlled, parallel-design study, transdermal testosterone patches (150 and 300 µg) in surgically menopausal, low-libido women treated with oral estrogen have been shown to be safe after 12 months of therapy. A previous publication has shown that the 300-µg transdermal testosterone patch improves sexual function in women who have undergone bilateral oophorectomy and hysterectomy.

Menopause, HRT, memory and Alzheimer's disease

Estrogens may have the potential to prevent or delay the onset of dementia, including Alzheimer's disease, through multiple neuroprotective, neurotrophic and neuromodulatory actions.

Observational and experimental studies of estrogen and memory in postmenopausal women do not show consistent cognitive improvements with HRT. Effects of estrogens on cognitive tests may be selective according to the test used and reproductive status of the women under study. Convergent evidence for the effects of estrogen on cognitive function comes from studies that have examined cognition in relation to menstrual cycle

phase, biomarkers of lifelong estrogen exposure, menopausal symptoms, estrogen receptor polymorphisms, neuroimaging studies and circulating hormone levels.

Meta-analyses of observational studies examining HRT and cognitive function suggest a significant reduction in the risk of Alzheimer's disease among women who have ever used HRT. There is some suggestion that estrogens may be more protective against Alzheimer's disease when used by younger postmenopausal women or when initiated at an earlier age. This suggestion finds some support in preliminary evidence that women who initiate HRT before the last menstrual period may show better verbal memory than postmenopausal women who initiate HRT later, but this possibility has not been examined directly. Data from several observational studies suggest that longer duration of therapy may confer greater protection against Alzheimer's disease. One recent study found a significant reduction in the risk of Alzheimer's disease for women who used HRT for 3–10 years. In the same study, the 'excess' risk of Alzheimer's disease when compared with age-equivalent men disappeared among women who received HRT for more than 10 years. Randomized clinical trial data from the Women's Health Initiative Memory Study (WHIMS)* and anticipated results from the Women's Health Initiative Study of Cognitive Aging (WHISCA) will address the issue of continuous combined HRT in women aged 65 and older, but the results might not necessarily apply to younger women, since younger women were not included in the trial. Firmer conclusions would be possible if future randomized clinical studies were to examine the effects of HRT on cognitive aging and dementia in women who initiate HRT earlier in the climacteric.

Specific polymorphisms of the estrogen receptor α may be associated with accelerated cognitive decline. However, to date it is not possible to predict which women are at increased risk of development of Alzheimer's disease, nor those who might preferentially respond to HRT in terms of improved cognitive function. Owing to the uncertainty of the data, HRT should not be prescribed solely to obtain cognitive enhancement.

In a large randomized trial of raloxifene, a selective estrogen receptor modulator (SERM), women assigned to raloxifene had a similar 3-year cognitive score performance compared with women assigned to placebo, but elderly women (> 70 years) treated with raloxifene showed improvements on tests of verbal memory and attention.

In addition, as part of this trial, there was no effect on the risk of developing dementia or mild cognitive impairment (MCI) for women taking raloxifene 60 mg/day. However, the administration of raloxifene 120 mg/day resulted in a 33% lower risk of developing MCI, 48% lower risk of developing Alzheimer's disease, and 37% lower risk of developing any cognitive decline (dementia plus MCI). However, as with estrogens, it is premature to prescribe raloxifene to women solely for the prevention of Alzheimer's disease.

HRT and Parkinson's disease

Basic science, as well as epidemiological and clinical evidence, suggests that estrogens may influence Parkinson's disease symptoms. The incidence and symptoms of Parkinson's disease are different in males and females. Drugs for Parkinson's disease have different effects in the two genders.

Although it has been suggested that the use of postmenopausal hormones is associated with a lower risk of Parkinson's disease, this is still uncertain, nor is it clear whether this may be attributable to estrogens alone or should also take into account metabolic interactions between hormones and other substances, as recently suggested for caffeine. The role of HRT in symptom severity or in response to levodopa has also been evaluated by various authors, but a lack of consensus emerges on the potential role of estrogens in the disease. The available studies are of insufficient duration, and more trials are needed. However, no specific contraindications exist to HRT use in women with Parkinson's disease.

HRT and schizophrenia

Estrogens are not etiologically relevant in schizophrenia, but they seem to act as a modulating factor. This may be indicated by the later age of onset of schizophrenia in fertile women, suggesting a protective effect of estrogens. Moreover, an excess of onset of schizophrenia after the menopause is observed, supporting this hypothesis. Additionally, women with schizophrenia

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*Note from the Editors: at the time the workshop was held the WHIMS data were still embargoed, and the discussants were unaware of the results of this trial. Since the results were not discussed by the panel and a consensus could not be reached, a separate analysis of these data in view of the available literature has been added at the end of this paper.

may show a deterioration of the course of the disease after the menopause.

Postmenopausal women with schizophrenia may show fewer negative symptoms and may need fewer neuroleptics when on estrogen replacement. It is not known whether progestins can antagonize the positive effects of estradiol.

CONCLUSIONS AND RECOMMENDATIONS

Practically every area of the human brain is sensitive to sex hormones, as appears from the wide distribution of sex hormone receptors. In addition, sex hormone production takes place in neuronal and glial cells all over the brain. Circulating sex hormones influence neuronal function in a large number of brain areas and types of neurons and glial cells. However, since the action of sex hormones may be either stimulatory or inhibitory, depending on age, sex, brain area and cell type, careful studies not only of the possible positive effects of sex hormone substitution on brain function, but also of its possible negative effects on some brain areas and cell types, are urgently needed.

Procedures which reduce body temperature, such as lowering the ambient temperature, dressing in layers and drinking cool drinks will be beneficial for hot flushes. Paced respiration, as practiced in yoga breathing, has been shown to reduce hot flush frequency by about 50%. Drugs which reduce central noradrenergic activation, such as clonidine, have about the same degree of effectiveness, but are limited by side-effects. A variety of isoflavones have not proved more effective than placebo. Although HRT is clearly the most effective treatment for hot flushes, the risk/benefit ratio must be evaluated individually for each patient.

To manage migraine at menopause, it may be convenient to use HRT in a continuous combined regimen. In addition, the transdermal route of estradiol administration seems to be the least invasive in terms of clinical expression of the disease.

The decision to prescribe estradiol for perimenopausal depression must be further informed by both the risks of estrogen replacement therapy and the availability of alternative treatments. The first-line medication for perimenopausal women presenting with depression would be a traditional antidepressant such as a selective serotonin re-uptake inhibitor. Treatment of depression with estradiol could be considered under the following circumstances: as an alternative for the 50% or so of ambulatory patients with depression who fail to respond to a conventional, first-line intervention; in women who refuse to take psychotropic agents or who otherwise prefer treatment with estradiol; in women who will undertake treatment with estradiol for other acute symptoms (e.g. hot flushes) and who, therefore, could delay treatment with antidepressants until determining whether estradiol treatment is sufficient. Estradiol treatment is no longer appropriate for prophylaxis; it is still reasonably prescribed for acute symptoms and syndromes, including depression. Additional research is needed to define the role of estrogen therapy in the management of depression. In addition, as a progestin can affect mood and induce depressive symptoms, further studies should be performed to understand the specific effects of natural progesterone as well as of the different synthetic progestins.

In postmenopausal women receiving sufficient estrogen treatment, the addition of androgenic compounds seems to be highly effective in managing sexual symptoms, such as low libido and lack of sexual pleasure. Tibolone, a tissue-specific compound, is able to restore sexual function, exerting both an estrogenic and an androgenic effect on genital tissues and central circuitries involved in sexual response. With an appropriate preparation specifically tailored for androgen replacement in postmenopausal women, the treatment of sexual dysfunction in women looks to be promising and safe. Additionally, DHEA supplementation seems to be promising for its estrogenic and androgenic effects, as well as its neuroendocrine actions, but further studies are needed to assess fully its efficacy and safety for postmenopausal replacement therapy.

Except after a surgical menopause, where there is limited clinical trial evidence that estrogen therapy may help maintain verbal memory, there is no consistent evidence that HRT has an effect on memory or other aspects of cognition. Observational data imply that HRT use may reduce Alzheimer's risk by about one-third. Findings from observational studies raise questions concerning the timing of HRT initiation and duration of HRT use in relation to cognition or dementia. However, evidence relating to these points is preliminary. Subgroup and secondary analyses from one large randomized trial imply that raloxifene, a SERM, may help to maintain select cognitive skills when used by women after the age of 70 years, and that high-dose raloxifene may protect against mild cognitive impairment.

However, it is premature to recommend SERMs for cognitive symptoms or prevention of Alzheimer's disease.

General effects of estrogens seem similar in Parkinson's disease and in healthy women, and eventual adverse effects on disease symptoms are usually soon perceived. Parkinson's disease and the menopause should therefore be considered as two distinct entities. Useful recommendations may be the use of transdermal rather than oral administration, in order to reduce possible pharmacological interferences with Parkinson's disease therapy and to avoid an increased number of daily pills.

Studies of estrogen replacement therapy in postmenopausal women with schizophrenia are urgently needed, as the course of this chronic recurrent disorder could hopefully be ameliorated by estradiol substitution. Also, studies of alternative regimens, e.g. estradiol substitution without progestogens or application of SERMs, should be undertaken.

SUGGESTED READING

Basic science

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POSTSCRIPT

A. R. Genazzani, M. Gambacciani, T. Simoncini and H. P. G. Schneider

When the Panel was revising the Position Paper, Shumaker and colleagues published the WHIMS – Women's Health Initiative Memory Study – that had enrolled more than 4500 postmenopausal women participating in the Women's Health Initiative (WHI) trial, randomly assigned to treatment with 0.625 mg conjugated equine estrogens (CEE) + 2.5 mg medroxyprogesterone acetate (MPA) or placebo. Participants were tested at baseline and annually using a standard mental state examination. Women treated with CEE + MPA had an increased risk for diagnosis of probable dementia compared with placebo. This increased risk resulted in 23 additional cases in 10 000 women per year. The authors regarded this risk as low, confined to elderly (65 years or older) women, but still recommended use of hormone treatment only for menopausal symptoms and not for dementia prevention. In addition, in the same issue of the *Journal of the American Medical Association*, Rapp and colleagues reported that, among postmenopausal women aged 65 years or older recruited to the WHIMS, estrogen plus progestin did not improve cognitive function when compared with placebo.

The WHIMS findings on global cognitive function do not address the possible role of HRT initiated before the age of 65 years. As stated by the authors, these conclusions, like those of the earlier reports of the WHI study, pertain to the specific strength formulation of hormone therapy

and not to different formulations or routes of administration. In the WHIMS, and in general in all the WHI population, the menopause had occurred even 20–25 years before study enrolment. The age and the menopausal age of the women involved in the WHIMS are important factors which could influence the study results. Therefore, WHI/WHIMS results pertain only to HRT initiated in the late postmenopausal period.

The WHIMS confirms the Cache County Study, published in 2002 by Zandi and colleagues. One result of this large, prospective, population-based study is the suggestion that early initiation and long-term continuation of HRT after the menopause may help to prevent Alzheimer's disease. Conversely, in women treated with hormones late after the menopause, effects on Alzheimer's disease risk may not be evident. The issue of a possible critical time of hormone administration was also raised in the accompanying Editorial by Resnick and Henderson. Therefore, the use of hormones in elderly women, as in the WHIMS, for a relatively short period (5.2 years) does not address the real effect of long-term (more than 5–10 years) HRT started as appropriate in symptomatic, early-postmenopausal women.

The results of the WHIMS contradict the strong biological, epidemiological and clinical evidence that supports the beneficial effects of estrogen on the brain. In the WHI/WHIMS reports, it has been stated that this trial involved predominantly healthy women. However, the age, the time since menopause and the physical conditions (body mass index, hypertension, etc.) are clearly in contrast with this statement. It is likely that, at this age, even 'healthy' women already have vascular disorders. Comparing the WHIMS results with the increased incidence of cardiovascular disease and stroke in the same patient cohort, analogies can be seen. Initiation of HRT at the dose used in the WHI study in elderly women can lead to destabilization of atherosclerotic plaques and other changes, which in turn lead to the increased incidence of vascular events (myocardial infarction, deep venous thrombosis and stroke) reported in the first year of HRT use. This correlates with the results concerning increase in dementia risk, which also begins after 1 year of treatment. Such 'co-incidence' suggests rather a vascular reason for this type of dementia. It is therefore questionable whether any preventive effects of HRT can be attained in elderly patients, who represent a cohort of women with long-term estrogen deficiency. The results of this randomized clinical trial cannot highlight the ultimate effect on the brain of long-term HRT initiated in appropriate doses and with appropriate timing, i.e. in a perimenopausal woman for the onset of climacteric symptoms.

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