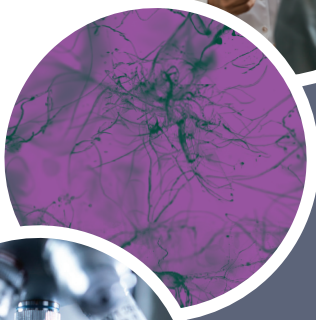


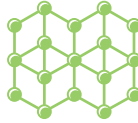
**Estrogen and
Neurodegenerative
& Neurovascular
Disease Processes:
Friend or Foe?**



**Estrogen and
Neurodegenerative
& Neurovascular
Disease Processes:
Friend or Foe?**



Terri DeNeui
DNP, APRN, ACNP-BC



This review will provide an in-depth, evidence-based perspective regarding endogenous and exogenous estradiol, and its relationship to neurodegenerative and neurovascular disease processes. After reviewing this paper and the literature presented, it will become apparent that not only does 17-beta-estradiol protect the neurovascular and neurological systems, but there is also no correlation between the use of non-oral 17 β estradiol preparations and stroke risk.

Further, recent studies have pointed to the role 17-beta-estradiol may play in the treatment of ischemic stroke and the prevention of vascular and Alzheimer's dementia.

The intention of this paper is to disseminate past and recent literature regarding these topics, thereby paving the way for an updated and more accurate collegial dialogue amongst clinicians, their peers, and governing boards. It is time we begin to look at factual data regarding stroke and stroke risk and stop relying on misguided "hormone therapy induced stroke theory" as a root cause or risk factor of ischemic stroke in postmenopausal women on estrogen therapy.
















Menopausal Hormone Therapy

Menopausal Hormone Therapy (MHT) refers to the hormones used in the management of postmenopausal hormone decline.

MHT may include the use of estrogen alone or in combination with micronized progesterone or progestin. Estrogens may be bioidentical or synthetic; progesterone is considered bioidentical and progestins are synthetic. The term "bioidentical" means the hormones in the product are plant sourced and are chemically identical to those the human body produces. Synthetic hormones are derived from man-made chemical compounds and are not chemically identical to those the human body produces.

Menopausal Hormone Therapy

Bioidentical	Route of Administration	Formulation
17β-estradiol	 Oral	<i>Tablet</i>
	 Non-Oral	
	 Transdermal	<i>Patch, Gel, Film, Spray</i>
	 Vaginal	<i>Cream, Ring, Tablets</i>
	 Subcutaneous	<i>Pellet</i>
Estradiol	 Vaginal	<i>Tablet, Ring, Injection</i>
	 Intramuscular	
Micronized Progesterone	 Oral	<i>Capsules, Cream, Ovules</i>
	 Vaginal	
Non-Bioidentical/Synthetic	Route of Administration	Formulation
Conjugated Estrogens (CEE)	 Oral	<i>Tablet, Vaginal Cream, Injection</i>
	 Vaginal	
	 Intramuscular	
Progestins (MPA)	 Oral	<i>Tablet</i>

(DeNeui, et.al.,2019)

**MHT & Cardiovascular
and Neurovascular
Disease/Stroke Risk:**

**How did we
get here?**



The Women's Health Initiative Trial (WHI) was a large, randomized clinical trial funded by the National Institutes of Health to determine if MHT prevented heart disease, breast and colorectal cancer, and osteoporotic fractures in postmenopausal women. The WHI launched at a time when observational studies suggested a protective effect of estrogen on the heart and bones of postmenopausal women. The initiative purpose was to determine if postmenopausal hormone therapy should be prescribed for cardio- and osteoporosis protection for all women. The study, which began in 1991 and was to end in 2005, included the MHT clinical trials, an observational study, and two extension studies from 2005–2010 and 2010–2015 (*Women's Health Initiative, 2017*).

Research goals for the WHI were to:

- 1) determine the efficacy of MHT on non-fatal myocardial infarction and death;
- 2) determine the safety or risk of MHT for invasive breast cancer; and
- 3) determine secondary outcomes on osteoporosis, stroke, pulmonary embolism, venous thromboembolism, colorectal cancer, endometrial cancer, and mortality (*DeNeui, et al., 2019*).



Women with previous hysterectomy (N=10,739) were randomized to conjugated equine estrogen, CEE (commonly known as Premarin) Women with previous hysterectomy (N=10,739) were randomized to conjugated equine estrogen, CEE (commonly known as Premarin) or placebo. For this group, the intervention lasted 7.2 years. Post-intervention follow-up was 6.6 years and cumulative follow-up was 13 years. Women with an intact uterus (N=16,608) were randomized to CEE + medroxyprogesterone acetate, MPA, (commonly known as Prempro) or to placebo. The intervention phase was 5.6 years, post-intervention follow-up was 8.2 years and cumulative follow-up was 13.2 years.

As it relates to the topic of this paper, preliminary results of the trial showed that compared to placebo, women in the CEE treatment group had an increased risk of stroke and blood clots.

These results propagated the grave misinformation that all forms of menopausal hormones (estrogens) have a single class effect and therefore “all forms of estrogen must have an increased risk of blood clots and stroke”. This misinformation, although refuted in the literature in dozens of clinical studies, continues to promulgate in mainstream and medical communities to this day.

The cost of estrogen avoidance data post WHI is astounding. Estrogen has rapid beneficial vascular effects in the cardio and neurovascular systems, and withdrawal of estrogen may result in clinically significant changes in arterial function, resulting an acute myocardial infarction and/or stroke (*Venetkoski, et.al., 2018*). In the Venetkoski, et.al., study of over 400,000 women on post-menopausal estrogen therapy, women younger than 60 years at discontinuation of HT showed a significantly increased risk of stroke death during the first year after treatment as compared with age matched female background population (*Venetkoski, et. al., 2018*). Data collected from Mikkola T., et al., evaluated the impact of of discontinuing hormone therapy on more than 330,000 women. Cessation of hormone therapy was shown to be accompanied with increased risk of death. The study further revealed women less than 60 years old had a two to threefold increased risk of cardiac and stroke mortality compared with the age-standardized background population death rate of the entire country after stopping MHT with estrogen (*Hodis & Mack, 2018*).

Current Guidelines for Menopausal Hormone Therapy

Association

Guidelines



THE NORTH AMERICAN
MENOPAUSE SOCIETY

North American Menopause Society (NAMS) Position (2017):

- Individualized approach
- No longer “lowest dose for shortest period of time”
- Use evidence-based information to determine the appropriate type, dose, formulation, route, and duration
- Should be based on the unique health risks of the woman and the goals of therapy



American College of Obstetrics and Gynecology (ACOG)

- ACOG guidelines suggest alternative forms of estrogen and progesterone to those investigated in WHI (CEE/ CEE+MPA) for vasomotor symptom relief as alternative forms may be associated with different risk and stroke/clotting profile than CEE and CEE+MPA



Estrogens for MHT: Is there a risk?



Evidence from systematic reviews and guidelines support estrogen as effective in treating moderate to severe vasomotor symptoms, symptomatic vaginal atrophy, and in preventing postmenopausal osteoporosis in women transitioning through menopause; estrogen therapy remains the gold standard for relief of menopausal symptoms (*DeNeui, et.al., 2019*).

Estrogens are available in many formulations and routes of administration, which have similar efficacy for symptom relief, although their metabolic effects, and side effect profiles differ greatly.

Although typically associated with female reproductive function, estrogens mediate physiological processes in nearly every body tissue. 17-beta-estradiol (17 β -E2) is the most prominent and potent estrogen in circulation and during the menopause transition and post menopause, the ovaries cease to produce 17 β -E2. Estrogens are lipophilic in nature and therefore cross the blood brain barrier easily and diffusely. Estrogen is a pleiotropic hormone that exerts protective actions on multiple tissues, including the brain, and the protective effects of estrogen carry tremendous implications for the promotion of health and the prevention of disease in postmenopausal women (*Dubal & Wise, 2002*).

Oral estrogen preparations metabolize via the 'first pass' mechanism through the liver, thereby reducing the systemic bioavailability of the hormone to 2-10%. The major differences between administrations of oral versus non-oral preparations lie in the metabolic changes produced by the first pass effect and are

expressed most notably in the cardiovascular and neurovascular systems. The first pass metabolism of oral estrogen has favorable effects on lipid parameters, insulin resistance and inflammatory markers, but less favorable effects on triglycerides and clotting factors (*DeNeui, et.al.,2019*).

Some oral estrogen formulations have been implicated in increasing the risk of clotting and concerns of the thrombotic potential of estrogen arose from early observations that oral contraceptives appeared to increase the risk of venous thrombosis, pulmonary embolism, and stroke (*Dubal & Wise, 2002*). We now know that the dose and the route of estrogen delivery are key components in determining clotting potential. At higher doses, oral estrogen, which is metabolized via a first pass through the liver, can stimulate the production of thrombogenic factors primarily through its actions in the liver; alternatively, non-oral delivery of estrogen bypasses this “first pass metabolism” through the liver and prevents estrogen induced thrombogenic factors in the liver (*Dubal & Wise, 2002*).

In a review of thrombotic risk and estrogen use by Canonico, it was shown non-oral estrogens, such as patches and subcutaneous pellets, are not associated with an increased clotting risk and biological data support this difference between oral and non-oral preparations (2015). Additionally, significant differences in clotting risk between estrogen hormone preparations relate to the simultaneous use of a synthetic progestin. Studies have consistently shown that clotting risk is higher among users of combined estrogens plus progestins than among users of estrogens alone or estrogens with oral micronized (bio-identical) progesterone (*Canonico, 2015*). A clinical study by Rovinski, et.al., mirrored these results, concluding that blood clotting risk was increased in postmenopausal women with no previous thromboembolic events using oral estrogen preparations, however non-oral preparations did not significantly affect this risk (2018).

Generally, non-oral, 17-beta estradiol delivery has more physiologic systemic effect and a decreased risk of deep vein thrombosis, stroke, and myocardial infarction, secondary to the decreased clotting risks compared to oral administration.

Studies comparing oral 17-beta estradiol to CEE showed greater risk of venous thromboembolism (VTE) and myocardial events in the CEE group, suggesting not only the route, but the type of estrogen administration may be important to consider (*DeNeui, et.al.,2019*).



**Estrogen,
Neurodegeneration &
Neurovascular Disease:
Root cause or
preventative?**

When discussing root cause and treatment options, risks, and benefits of certain therapies as it relates to stroke, it is important to understand what constitutes a stroke. Ischemic stroke is characterized by an abrupt deprivation of blood flow, oxygen, and vital nutrients to the brain that quickly leads to cell death, known as apoptosis (Wise, et.al., 2005). The ischemic cascade also involves an inflammatory response triggered by damage-associated molecular patterns (DAMPs) released from the dying cells which trigger activation and recruitment of immune cells (Petrone, et.al., 2015). This environment of immune cells secretes pro-inflammatory cytokines that not only act locally in the brain but also may enter the systemic blood circulation to trigger a systemic immune response (Petrone, et.al., 2014; Petrone, et.al., 2015). Understanding the downstream effects of ischemic stroke induced inflammatory immune response may help explain why estradiol, as a potent immunomodulator, may not only prevent ischemic stroke, but also play a role in treatment.

Estrogen is the most extensively studied of the sex hormones in both laboratory and clinical settings and is considered increasingly to be an endogenous neuroprotective agent; further, many studies have shown that exogenous estrogen use reduces ischemia in both sexes (Hurn & Macree, 2000; Brown, et.al., 2009). Estrogen has

immunomodulating and anti-inflammatory effects in numerous body systems, most notably the neurovascular system, and several studies have shown that estrogen, specifically 17 β -E2, protects the brain from ischemic injury following stroke (Petroni, et.al., 2014; Singh, et.al., 2006; Suzuki et.al., 2009).

Brown, et.al., reported 17 β -estradiol “powerfully protects the brain using multiple molecular mechanisms that promote decreased cell death, increased neurogenesis, enhanced neurotrophic support, and the suppression of pro-inflammatory pathways” (2009). The evidence that estradiol stimulates neurogenesis (new nerve tissue) in the adult ischemic brain suggest that **estradiol therapy may facilitate the brain to undergo repair and remodeling after stroke** (Brown, et.al., 2009). Estrogen elicits effects through the estrogen receptor (ER) and the brain is rich with estrogen receptors, owing to the impact estradiol has in neurological and neurovascular function. ER alpha is critical in estradiol-mediated protection of the brain after stroke injury (Wise, et.al., 2005) and treatment with estradiol promotes rapid upregulation of the ER alpha (Brown, et.al., 2009).

Because the immune response following a stroke dictates recovery and the degree of brain damage, estrogen may be dually protective by also mediating the immune response. There are multiple mechanisms of 17 β -E2's neuroprotection, including activation of several neuroprotective pathways in the brain, but 17 β -E2 also mediates the local and systemic immune response to ischemic stroke through the estrogen receptor. Estrogen is a powerful antioxidant; however, analogs of estradiol (synthetic estrogens) do not appear to exert the same antioxidant effect as 17 β -E2. One theory is because synthetic analogs do not activate the estrogen receptor pathways, which are responsible for inducing the protective effects of estradiol (Petroni, et.al., 2015).

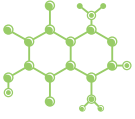
Another mechanism by which estrogen may reduce stroke risk is through modifying risk factors that underlie both stroke and coronary heart disease (CHD) such as the beneficial effects on diabetes and serum lipid profiles (Dubal & Wise, 2002). Further, CHD doubles the risk for stroke and estrogen therapy greatly reduces the risk for CHD up to 40%, thus it follows that estrogen may decrease the risk for stroke in parallel with its protective actions on CHD (Dubal & Wise, 2002). Of grave concern is the impact of prolonged estrogen deprivation in postmenopausal women untreated with MHT and is now considered a critical health matter as we realize that these women are at increased risk for chronic and acute disease processes such as dementia, stroke and myocardial infarction (Dubal & Wise, 2002).

In a landmark 2022 paper, the authors concluded not only does estradiol play a critical role in the neurobiology of aging, but also that there are complex interactions between estradiol and the other sex hormones- chiefly testosterone and progesterone (*Jett, et.al., 2022*). Brain imaging studies demonstrated that middle-aged women exhibit increased indicators of Alzheimer's disease (AD) endophenotype as compared to men of the same age, with onset in perimenopause (*Jett, et.al., 2022*). The authors demonstrated with baseline PET scans at the onset of perimenopause, and repeat scans 3 years post menopause, the beta amyloid deposition, hallmark of AD, was evident with no clinical signs and symptoms of dementia yet present (*Jett, et.al., 2022*).

Estrogen receptors at the brain level are abundant in the hypothalamus, thermoregulatory and sleep and circadian cycle centers as well as fundamental regions for learning and memory; they also participate at the brain level in the modulation of neural differentiation, neuroinflammation, synaptic plasticity, proliferation, behavior, and cholesterol metabolism (*Carrera-Gonzales, et.al., 2023*). Endocrine aging has been found to accelerate chronological aging in the brain of women years before the onset of AD symptoms and estrogens have neuroprotective effects that are mostly eliminated with the drastic systemic decrease in estradiol during peri and post menopause (*Carrera-Gonzales, et.al., 2023*).

As the sex hormones begin to decline in most women in their 30's, starting with testosterone; followed by a reduction in progesterone in their 40's, and reaching peak decline when estradiol begins to fluctuate in the perimenopause, it is vital to replace each hormone as soon as evident, not waiting for the woman to become post-menopausal. The authors of both previous papers concluded the use of hormone therapy would not only alleviate the symptoms of depression and cognitive impairment associated with menopause but would also prevent the risk of dementia.

Lastly, as it relates to brain aging and disease prevention and the use of MHT, it is imperative to understand the protective benefits discussed herein (neuroinflammation, immunomodulation, protection against apoptosis, beta amyloid and subsequent neurodegeneration), are chiefly evident depending on the type of compounds used. Progestins and synthetic estrogens have vastly different and opposing outcomes in neuroprotection, inflammation and immunomodulation than do 17beta estradiol and progesterone (*Wise, et.al., 2023*).



Conclusion

It is vitally important clinicians understand the physiologic sequelae in ischemic stroke and other neurodegenerative disease states and the positive role estrogen plays in both sexes. Clinicians must also take a closer look at root causes of stroke (and AD), such as lifestyle factors that cause systemic inflammation as well as epigenetic influences, prior to generalizing opinions regarding MHT and stroke risk. Systemic inflammation is associated with an increased risk of ischemic stroke (*Petrone, et.al., 2015*), the primary causes of systemic inflammation being lifestyle factors such as smoking, stress and diet.

Although some studies have shown a slight increased risk of thrombotic events in postmenopausal women taking certain oral estrogen preparations, timing since menopause, co-morbidities, and lifestyle factors such as smoking, and weight were all variables to consider. Notably, non-oral preparations, such as patches, subcutaneous pellets and others, have not been shown in any clinical study to increase thrombotic or ischemic stroke risk.

Estradiol is a potent immunomodulator and powerful anti-inflammatory agent, both functions of which are vital for stroke prevention and post stroke recovery. Clinical studies have shown estrogen replacement in postmenopausal women to ameliorate cognitive dysfunction, decrease the risk and delay the onset of degenerative conditions such as Alzheimer's disease and stroke (*Carrera, et.al., 2023; Dubal & Wise, 2002; Wise, et.al., 2023*). Estradiol has also been shown to favorably alter lipid parameters, prevent osteoporosis and cardiovascular disease, decrease, or eliminate depression, and improve overall quality of life.

Considering the chronic and acute disease risk posed to postmenopausal women avoiding MHT, it is essential clinicians give their patients seeking relief from menopausal hormone decline individualized, accurate information regarding disease prevention and risk, and the differences between the modalities of MHT from which to make the life altering decision of whether to initiate hormone therapy or not. It is equally important for the governing boards of clinicians to be up to date regarding the literature in this arena, enabling an adequate and accurate evaluation of any clinical cases involving MHT presented for review.

Bibliography

1. Brann, D. W., Dhandapani, K., Wakade, C., Mahesh, V. B., & Khan, M. M. (2007). Neurotrophic and neuroprotective actions of estrogen: basic mechanisms and clinical implications. *Steroids*, 72(5), 381-405.
2. Brann, D., Raz, L., Wang, R., Vadlamudi, R., & Zhang, Q. (2012). Oestrogen signalling and neuroprotection in cerebral ischaemia. *Journal of neuroendocrinology*, 24(1), 34-47.
3. Brown, C. M., Suzuki, S., Jelks, K. A., & Wise, P. M. (2009, May). Estradiol is a potent protective, restorative, and trophic factor after brain injury. In *Seminars in reproductive medicine* (Vol. 27, No. 03, pp. 240-249). © Thieme Medical Publishers.
4. Canonico, M. (2015). Hormone therapy and risk of venous thromboembolism among postmenopausal women. *Maturitas*, 82(3), 304-307.
5. Canonico, M., Oger, E., Conard, J., Meyer, G., Lévesque, H., Trillot, N., ... & ESTrogen and THromboEmbolism Risk (ESTHER) Study Group. (2006). Obesity and risk of venous thromboembolism among postmenopausal women: differential impact of hormone therapy by route of estrogen administration. The ESTHER Study. *Journal of Thrombosis and Haemostasis*, 4(6), 1259-1265.
6. Carrera-González, M. P., Ramírez-Expósito, M. J., Guerrero-González, C., & Martínez-Martos, J. M. (2023). Alzheimer's disease: Is there a relationship between brain renin-angiotensin system, estradiol and glucose transporter-4 (GLUT-4)? *AIMS Molecular Science*, 10(1), 37-51.
7. DeNeui, T., Berg, J., & Howson, A. (2019). Best practices in care for menopausal patients: 16 years after the Women's Health Initiative. *Journal of the American Association of Nurse Practitioners*, 31(7), 420-427.
8. de Tassigny, X. D. A. (2017). Outlook on the neuroprotective effect of estrogen. *Neural regeneration research*, 12(11), 1799.
9. Dubal, D. B., & Wise, P. M. (2002). Estrogen and neuroprotection: from clinical observations to molecular mechanisms. *Dialogues in clinical neuroscience*.
10. Engler-Chiurazzi, E. B., Brown, C. M., Povroznik, J. M., & Simpkins, J. W. (2017). Estrogens as neuroprotectants: estrogenic actions in the context of cognitive aging and brain injury. *Progress in neurobiology*, 157, 188-211.
11. Etgen, A. M., Jover-Mengual, T., & Zukin, R. S. (2011). Neuroprotective actions of estradiol and novel estrogen analogs in ischemia: translational implications. *Frontiers in neuroendocrinology*, 32(3), 336-352.
12. Guo, H., Liu, M., Zhang, L., Wang, L., Hou, W., Ma, Y., & Ma, Y. (2020). The critical period for neuroprotection by estrogen replacement therapy and the potential underlying mechanisms. *Current Neuropharmacology*, 18(6), 485-500.

13. Henderson, V. W. (2014). Alzheimer's disease: review of hormone therapy trials and implications for treatment and prevention after menopause. *The Journal of steroid biochemistry and molecular biology*, 142, 99-106.
14. Hodis, H. N., & Mack, W. J. (2018). Cardiovascular risk after withdrawal of hormone therapy. *Menopause*, 25(4), 365-367.
15. Hurn, P. D., & Macrae, I. M. (2000). Estrogen as a neuroprotectant in stroke. *Journal of Cerebral Blood Flow & Metabolism*, 20(4), 631-652.
16. Hurn, P. D., & Brass, L. M. (2003). Estrogen and stroke: a balanced analysis. *Stroke*, 34(2), 338-341.
17. Inagaki, T., & Etgen, A. M. (2013). Neuroprotective action of acute estrogens: animal models of brain ischemia and clinical implications. *Steroids*, 78(6), 597-606.
18. Jett, S., Schelbaum, E., Jang, G., Boneu Yopez, C., Dyke, J. P., Pahlajani, S., ... & Mosconi, L. (2022). Ovarian steroid hormones: A long overlooked but critical contributor to brain aging and Alzheimer's disease. *Frontiers in Aging Neuroscience*, 14, 786.
19. Lebesgue, D., Chevaleyre, V., Zukin, R. S., & Etgen, A. M. (2009). Estradiol rescues neurons from global ischemia-induced cell death: multiple cellular pathways of neuroprotection. *Steroids*, 74(7), 555-561.
20. Liu, R., & Yang, S. H. (2013). Window of opportunity: estrogen as a treatment for ischemic stroke. *Brain research*, 1514, 83-90.
21. Lobo, R. A., Pickar, J. H., Stevenson, J. C., Mack, W. J., & Hodis, H. N. (2016). Back to the future: hormone replacement therapy as part of a prevention strategy for women at the onset of menopause. *Atherosclerosis*, 254, 282-290.
22. Luine, V. N. (2014). Estradiol and cognitive function: past, present and future. *Hormones and behavior*, 66(4), 602-618.
23. Mahmoodzadeh, S., Leber, J., Zhang, X., Jaisser, F., Messaoudi, S., Morano, I., ... & Regitz-Zagrosek, V. (2014). Cardiomyocyte-specific estrogen receptor alpha increases angiogenesis, lymphangiogenesis and reduces fibrosis in the female mouse heart post- myocardial infarction. *Journal of cell science & therapy*, 5(1), 153.
24. Menazza, S., & Murphy, E. (2016). The expanding complexity of estrogen receptor signaling in the cardiovascular system. *Circulation research*, 118(6), 994-1007.
25. Mikkola, T. S., Savolainen-Peltonen, H., Tuomikoski, P., Hoti, F., Vattulainen, P., Gissler, M., & Ylikorkala, O. (2016). Lower death risk for vascular dementia than for Alzheimer's disease with postmenopausal hormone therapy users. *The Journal of Clinical Endocrinology & Metabolism*, 102(3), 870-877.
26. Mikkola, T. S., Tuomikoski, P., Lyytinen, H., Korhonen, P., Hoti, F., Vattulainen, P., ... & Ylikorkala, O. (2015). Estradiol-based postmenopausal hormone therapy and risk of cardiovascular and all-cause mortality. *Menopause*, 22(9), 976-983.
27. Mikkola, T. S., Tuomikoski, P., Lyytinen, H., Korhonen, P., Hoti, F., Vattulainen, P., ... & Ylikorkala, O. (2015). Increased cardiovascular mortality risk in women

discontinuing postmenopausal hormone therapy. *The Journal of Clinical Endocrinology & Metabolism*, 100(12), 4588-4594.

28. Olié, V., Canonico, M., & Scarabin, P. Y. (2010). Risk of venous thrombosis with oral versus transdermal estrogen therapy among postmenopausal women. *Current opinion in hematology*, 17(5), 457-463.
29. Pabon, M., Tamboli, C., Tamboli, S., Acosta, S., De La Pena, I., Sanberg, P. R., ... & Borlongan, C. V. (2014). Estrogen replacement therapy for stroke. *Cell medicine*, 6(3), 111-122.
30. Panay, N., Hamoda, H., Arya, R., & Savvas, M. (2013). The 2013 British menopause society & women's health concern recommendations on hormone replacement therapy. *Menopause international*, 19(2), 59-68
31. Petrone, A. B., Simpkins, J. W., & Barr, T. L. (2014). 17 β -estradiol and inflammation: implications for ischemic stroke. *Aging and disease*, 5(5), 340.
32. Petrone, A. B., Rudy, C. C., Barr, T. L., Simpkins, J. W., & Reed, M. N. (2015). Neuroprotective effects of estrogen following neural injury. In *Estrogen Effects on Traumatic Brain Injury* (pp. 91-111).
33. Pike, C. J. (1999). Estrogen Modulates Neuronal Bcl-xl Expression and β -Amyloid-Induced Apoptosis: Relevance to Alzheimer's Disease. *Journal of neurochemistry*, 72(4), 1552- 1563.
34. Raghava, N., Das, B. C., & Ray, S. K. (2017). Neuroprotective effects of estrogen in CNS injuries: insights from animal models. *Neuroscience and neuroeconomics*, 6, 15.
35. Roger NJ Smith/John WW Studd et al Recent Advances in Hormone Replacement Therapy, *British Journal of Hospital Medicine*, 1993
36. Roach, R. E. J., Lijfering, W. M., Helmerhorst, F. M., Cannegieter, S. C., Rosendaal, F. R., & van Hylckama Vlieg, A. (2013). The risk of venous thrombosis in women over 50 years old using oral contraception or postmenopausal hormone therapy. *Journal of Thrombosis and Haemostasis*, 11(1), 124-131.
37. Rosano, G. M., Leonardo, F., Dicandia, C., Sheiban, I., Pagnotta, P., Pappone, C., & Chierchia, S. L. (2000). Acute electrophysiologic effect of estradiol 17 β in menopausal women. *American Journal of Cardiology*, 86(12), 1385-1387.
38. Rovinski, D., Ramos, R. B., Fighera, T. M., Casanova, G. K., & Spritzer, P. M. (2018). Risk of venous thromboembolism events in postmenopausal women using oral versus non- oral hormone therapy: a systematic review and meta-analysis. *Thrombosis research*, 168, 83-95.
39. Renoux, C., Dell'Aniello, S., & Suissa, S. (2010). Hormone replacement therapy and the risk of venous thromboembolism: a population-based study. *Journal of Thrombosis and Haemostasis*, 8(5), 979-986.
40. Salpeter, S. R., Cheng, J., Thabane, L., Buckley, N. S., & Salpeter, E. E. (2009). Bayesian meta-analysis of hormone therapy and mortality in younger postmenopausal women. *The American journal of medicine*, 122(11), 1016-1022.

41. Sarrel, P. M., Njike, V. Y., Vinante, V., & Katz, D. L. (2013). The mortality toll of estrogen avoidance: an analysis of excess deaths among hysterectomized women aged 50 to 59 years. *American journal of public health*, 103(9), 1583-1588.
42. Scarabin, P. Y. (2018). Progestogens and venous thromboembolism in menopausal women: an updated oral versus transdermal estrogen meta-analysis. *Climacteric*, 21(4), 341-345.
43. Schreihofner, D. A., & Ma, Y. (2013). Estrogen receptors and ischemic neuroprotection: who, what, where, and when?. *Brain research*, 1514, 107-122.
44. Scott, E., Zhang, Q. G., Wang, R., Vadlamudi, R., & Brann, D. (2012). Estrogen neuroprotection and the critical period hypothesis. *Frontiers in neuroendocrinology*, 33(1), 85-104.
45. Simpkins, J. W., Singh, M., Brock, C., & Etgen, A. M. (2012). Neuroprotection and estrogen receptors. *Neuroendocrinology*, 96(2), 119-130.
46. Singh, M., Dykens, J. A., & Simpkins, J. W. (2006). Novel mechanisms for estrogen-induced neuroprotection. *Experimental Biology and Medicine*, 231(5), 514-521.
47. Sribnick, E. A., Ray, S. K., & Banik, N. L. (2004). Estrogen as a multi-active neuroprotective agent in traumatic injuries. *Neurochemical research*, 29(11), 2007-2014.
48. Suzuki, S., Brown, C. M., & Wise, P. M. (2009). Neuroprotective effects of estrogens following ischemic stroke. *Frontiers in neuroendocrinology*, 30(2), 201-211.
49. Tuomikoski, P., Salomaa, V., Havulinna, A., Airaksinen, J., Ketonen, M., Koukkunen, H., ... & Mikkola, T. S. (2016). Decreased mortality risk due to first acute coronary syndrome in women with postmenopausal hormone therapy use. *Maturitas*, 94, 106-109.
50. Venetkoski, M., Savolainen-Peltonen, H., Rahkola-Soisalo, P., Hoti, F., Vattulainen, P., Gissler, M., ... & Mikkola, T. S. (2018). Increased cardiac and stroke death risk in the first year after discontinuation of postmenopausal hormone therapy. *Menopause*, 25(4), 375-379.
51. Wise, P. M., Dubal, D. B., Rau, S. W., Brown, C. M., & Suzuki, S. (2005). Are estrogens protective or risk factors in brain injury and neurodegeneration? Reevaluation after the Women's health initiative. *Endocrine reviews*, 26(3), 308-312.
52. Wise, P. M., Suzuki, S., & Brown, C. M. (2023). Estradiol: a hormone with diverse and contradictory neuroprotective actions. *Dialogues in clinical neuroscience*.
53. Yoon, B. K., Chin, J., Kim, J. W., Shin, M. H., Ahn, S., Lee, D. Y., ... & Na, D. L. (2018). Menopausal hormone therapy and mild cognitive impairment: a randomized, placebo-controlled trial. *Menopause*, 25(8), 870-876.



920 S. Kimball Ave Ste 100 • Southlake, Texas 76092

www.EVEXIAS.com