Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

17α-Estradiol

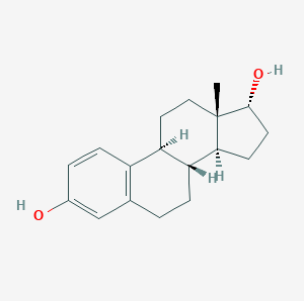
Evidence Summary

Compelling for its anti-aging, anti-inflammatory, and pro-cognitive properties, but the evidence is limited to preclinical studies.

Neuroprotective Benefit: Strong Aβ-decreasing, anti-inflammatory, and pro-cognitive properties of 17α-estradiol offer promise for neuroprotection, but evidence is limited to preclinical studies.

Aging and related health concerns: 17α-estradiol significantly increases lifespan in male mice, even when treatment is started late in life. These effects are accompanied by decreased body weight and improved metabolism. But no data exist in humans yet.

Safety: Based on one safety trial in postmenopausal women and several trials of topical formulations in people with hair loss, side effects were rare and mild. No safety data exists for long-term oral treatment in humans.

Availability: not available; research use only	**Dose**: Dose has not been established. In mouse lifespan studies, 14.4 ppm (14.4 mg in 1 kg of food) has been used.	**Chemical formula:** $C_{185}H_{24}O_2$ **MW**: 272.4  Source: PubChem
Half life: not reported	**BBB**: penetrant	
Clinical trials: none available, except a few clinical studies of topical formulations of 17α-estradiol for hair loss	**Observational studies**: none available	

What is it? 17α-estradiol is a naturally-occurring isomer of 17β-estradiol, the primary female sex hormone in women. In contrast to 17β-estradiol, 17α-estradiol is thought to be a non-feminizing estrogen with significantly reduced binding affinity for the classic estrogen receptors, ERα and ERβ (Toran-Allerand et al., 2002). 17α-estradiol is likely to be the predominant ligand for the estrogen receptor X (ER-X). 17α-estradiol is a minor component (~5%) of the hormone replacement medication Premarin™.

Neuroprotective Benefit: Strong Aβ-decreasing, anti-inflammatory, and pro-cognitive properties of 17α-estradiol offer promise for neuroprotection, but evidence is limited to preclinical studies.

Types of evidence: (bullet points)

- 0 meta-analyses or systematic reviews
- 0 clinical trials or observational studies
- 5 laboratory studies, 2 in AD mouse models, 2 in rats, and 1 in cell culture
- 1 laboratory study of a prodrug that increases 17α-estradiol levels selectively in the brain

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?: None available.

Human research to suggest benefits to patients with dementia: None available.

Mechanisms of action for neuroprotection identified from laboratory and clinical research: All studies examining the neuroprotective effects of 17α-estradiol have been carried out in rodents, and it is currently unknown whether similar benefits can be expected in people.

In a mouse model of Alzheimer's disease (AβPPswe transgenic mice), 17α-estradiol treatment for 6 weeks (~0.8 mg total across 6 weeks) decreased Aβ levels by 38%, which was greater than the effect seen with 17β-estradiol (27%) (Levin-Allerhand et al., 2002). In another study, middle-aged Alzheimer's model mice (APPswePS1 mice) treated with 17α-estradiol for 60 days (sustained release of up to 1.5 mg total across 60 days) had significantly reduced inflammation (microglial activation) and neuronal loss in the hippocampus (Manaye et al., 2011). Cell culture studies also show that 17α-estradiol pretreatment prevents the increase in cellular calcium levels that result from an Aβ insult (Kawahara and Kuroda, 2001).

In rats, 17β-estradiol and 17α-estradiol were equally protective against cognitive deficits (induced by a drug, scopolamine) and both had significant antioxidant and anti-inflammatory activities (decreased MDA and nitrite levels, increased SOD levels, and decreased TNFα) (Kaur et al., 2015). It is worth noting that 17α-estradiol appeared more effective than 17β-estradiol at reducing nitrite levels.

Roberta Diaz Brinton has proposed the "healthy cell bias" hypothesis of estrogen actions in the brain, which suggests that estrogens are protective in healthy cells but may be harmful in diseased states (Yao et al., 2012). For example, in cell culture, 17β-estradiol is protective when applied prior to or during Aβ42 insult. It is not protective if applied after—and exacerbates Aβ42-induced apoptosis. It is currently unknown if this "healthy cell bias" extends to women and/or to 17α-estradiol.

10β,17α-dihydroxyestra-1,4-dien-3-one (α-DHED), a bioprecursor prodrug that produces 17α-estradiol selectively in the brain, is under development (Prokai-Tatrai et al., 2018). Given the potential risks of feminization or effects on reproductive organs (e.g., uterotrophic effect), there are benefits to selectively increasing 17α-estradiol in the brain without affecting peripheral levels. α-DHED does not have affinities to 2 nuclear estrogen receptors, ERα and ERβ, and does not alter blood 17α-estradiol levels or exhibit uterotrophic effects. Although this study examined the antidepressant effects of α-DHED, there have not been any studies on its effects on cognitive functions.

APOE4 interactions: Unknown

Aging and related health concerns: 17α-estradiol significantly increases lifespan in male mice, even when treatment is started late in life. These effects are accompanied by decreased body weight and improved metabolism. But no data exist in humans yet.

Types of evidence:

- 0 meta-analyses or systematic reviews
- 0 clinical trials or observational studies
- 5 laboratory studies, 2 on mouse lifespan, 1 on metabolism and inflammation, and 1 on ischemia
- 2 reviews

Lifespan: POTENTIAL BENEFIT IN MALES BASED ON RODENT STUDIES

The National Institute on Aging Interventions Testing Program (NIA ITP) is designed to test compounds such as 17α-estradiol that are purported to extend lifespan and/or delay onset of age-related diseases. This program is a collaborative effort that uses 1) parallel studies in males and females at 3 different sites, 2) genetically heterogeneous mice (UM-HET3 mice) to guard against conclusions based on a single inbred genotype, and 3) enough samples to provide statistical power.

In the 2014 report, the genetically heterogeneous UM-HET3 mice were fed 4.8 mg/kg/day of 17α-estradiol from 10 months of age (Harrison et al., 2014). While the median lifespan pooled across 3 test sites showed that 17α-estradiol increased lifespan by 12%, this effect was driven primarily by one test site that showed a 28% extension compared to the two other test sites that showed an increase by only 3%. Interestingly, median lifespan increased in males but not in females. Hepatic lipidosis (fatty liver) decreased in males from 27% to 6%, but was unchanged in females, which may partly explain the preferential benefits on male survival. A potential confound was the short lifespan of the male controls at 2 out of the 3 test sites, while control female lifespan was long and comparable across 3 sites. While the reasons are unknown, the shorter lifespan in control males may have partly contributed to the proportionally larger lifespan extension with 17α-estradiol.

In a follow-up study published in 2016, the dose of 17α-estradiol was increased 3-fold to 14.4 mg/kg/day, which increased median lifespan by 19% in male mice (Strong et al., 2016). The effect was significant at all 3 sites (26, 9, and 23%). Similar to the previous study, there were no significant effects on female mice survival. Interestingly, males treated with 17α-estradiol lived longer on average than females (control or 17α-estradiol-treated). The potential mechanisms of action were not directly

correlated with lifespan, but may include improved metabolic function and decreased inflammation, described below.

In another follow-up study, male mice, castrated mice, female mice, and ovariectomized female mice were treated with 17α-estradiol (14.4 ppm in diet) started at 4 months of age (Garratt et al., 2017). Male-specific lifespan extension with 17α-estradiol was associated with increased insulin sensitivity and improved glucose tolerance. Females mice did not derive these metabolic benefits from 17α-estradiol. Male-specific metabolic improvements are associated with enhanced hepatic mTORC2 signaling (increased pNDRG1 and pSGK1 in males but not females), increased Akt activity, and phosphorylation of FOXO1a, changes that might promote metabolic health and survival in males. Castrated males showed fewer metabolic responses to 17α-estradiol compared to intact males, while ovariectomized females showed some responses similar to those seen in intact males. These findings suggest that gonadally derived hormones may contribute to sexual dimorphism in 17α-estradiol-induced lifespan extending effects.

In the most recent NIA ITP follow-up study, UM-HET3 mice treated with 17α-estradiol (14.4 ppm in diet) started at 16 and 20 months of age (roughly equivalent to humans of 50 and 60 years of age, respectively) extended median male lifespan by 19% ($p<0.0001$) and 11% ($p=0.007$), respectively (Harrison et al., 2021). Also, 90th percentile lifespans were extended 7% ($p=0.004$) and 5% ($p=0.17$), respectively. Body weights were reduced by about 20%. It is encouraging that lifespan extension benefits in males occurred even when 17α-estradiol administration was initiated at middle- or old-age. Initiating 17α-estradiol treatment at 16 months of age tended to increase lifespans more than starting treatment at 20 months; however, this difference reached statistical significance only at 1 of the 3 testing sites.

Only male mice had elevated levels of two conjugated estriols when given 17α-estradiol (Garratt et al., 2018). These findings suggest that males, but not females, metabolize 17α-estradiol into one or more estriol derivatives and that the sex-specific beneficial effects may be due to an estriol derivative rather than due to 17α-estradiol itself. The NIA ITP is pursuing this hypothesis and investigating whether male and female mice given diets containing estriol have extended lifespans.

Weight loss/Metabolism: POTENTIAL BENEFIT IN MALES BASED ON RODENT STUDIES
Male mice receiving 4.8 mg/kg/day of 17α-estradiol from 10 months of age were on average ~10% lighter at 12, 18, and 24 months of age compared to controls (Harrison et al., 2014). Females treated with 17α-estradiol were ~7% lighter than controls.

17α-estradiol alleviates age-related metabolic and adipose tissue dysfunction in mice (Stout et al., 2016). In aged male mice (18 and 20 months old), 17α-estradiol prevents the increase in body mass and visceral adiposity by decreasing leptin, energy intake, fasting glucose, insulin and liver triglycerides, and increasing insulin sensitivity. In the brain, 17α-estradiol increases hypothalamic mRNA levels of anorexigenic genes (ERα, leptin receptor, melanocortin 4 receptor, POMC). Some of the effects of 17α-estradiol, such as increased AMPK activity and reduced mTOR activity, are similar to those seen with caloric restriction (Newman et al., 2016).

In old male mice fed a high-fat diet, 17α-estradiol administration elicited beneficial effects on metabolism by quickly reducing caloric intake and initiating weight loss without altering locomotor activity or metabolic rate (Steyn et al., 2018). There was also significantly enhanced glucose tolerance, decreased insulin secretion during an intraperitoneal glucose challenge, and reductions in fasting glucose and insulin levels. Reductions in body mass was mostly attributed to significant declines in fat mass while sparing lean mass. These effects of 17α-estradiol occur via hypothalamic pathways, specifically through increasing pro-opiomelanocortin (Pomc) expression in the arcuate nucleus to reduce food intake and body mass. Pomc-expressing neurons located within the arcuate nucleus constitute an anorexigenic node of appetite regulating neurons; activation of these neurons promotes satiety and diminishes food intake.

In UM-HET3 mice, treatment with 17α-estradiol (14.4 ppm in diet) for 8 months generates sex-specific changes in the metabolomic profile of the liver and plasma (Garratt et al., 2018). In males, 17α-estradiol treatment raised the abundance of several amino acids in the liver, and this was associated with elevations in metabolites involved in urea cycling, whereas in females, amino acids and urea cycling metabolites were unaffected.

In male mice, treatment with 17α-estradiol (14.4 ppm in diet) increases hepatic IGF1 production without altering growth hormone secretion and uncouples IGF1 production from insulin sensitivity (Sidhom et al., 2020). In contrast, no effects in female IGF1 production are observed following 17α-estradiol treatment. In growth hormone receptor knockout (GHRKO) male mice, the induction of hepatic IGF1 by 17α-estradiol is dependent upon growth hormone signaling. Based on these studies, IGF1 reduction is not necessary to improve male longevity since 17α-estradiol extends lifespan in male mice despite increasing IGF1.

In genetically heterogeneous UM-HET3 mice, treatment with 17α-estradiol (14.4 ppm in diet) started at middle- to old-age (16 and 20 months of age; roughly equivalent to humans of 50 and 60 years of age, respectively) decreased body weight by 20% (Harrison et al., 2021).

Inflammation: MIXED.
In aged male mice (18 months old), 17α-estradiol treatment for 15 weeks decreased inflammation in adipose tissue (TNFα, IL-6, MCP-1, IL-1α, IL-1β)(Stout et al., 2016). However in a more recent study, UM-HET3 mice treated with 17α-estradiol (14.4 ppm in diet) started at 9 months of age did not alter gonadal white adipose tissue or adipose tissue inflammation (Mau et al., 2020).

Ischemia: POTENTIAL BENEFIT BASED ON A STUDY IN RAT.
In a rat model of ischemia (middle cerebral artery occlusion), 17α-estradiol pretreatment (24 hours prior to occlusion) significantly improved survival rate and substantially reduced brain lesion size by 55-81% (Simpkins et al., 1997). The magnitude of benefit was similar to that observed with 17β-estradiol pretreatment. 17β-estradiol post-treatment (40 min post-occlusion) also decreased mortality and lesion size—17α-estradiol was not tested in these experiments.

Liver disease: POTENTIAL BENEFIT BASED ON RODENT STUDIES
In male mice, treatment with 17α-estradiol (14.4 ppm in diet) improved liver disease pathology in an ERα-dependent manner by decreasing liver mass, fatty acids, and triglycerides (Mann et al., 2020). Acute 17α-estradiol administration also improved hepatic insulin sensitivity in male rats. Benefits of 17α-estradiol, as measured by fasting insulin, HbA1c, glucose tolerance test, are attenuated with ERα ablation.

Muscle strength: POTENTIAL BENEFIT BASED ON RODENT STUDIES
In UM-HET3 mice, treatment with 17α-estradiol (14.4 ppm in diet) started at 4 months of age diminishes body weight in both sexes, while treatment started at 16 months of age results in better retention of body weight (Garratt et al., 2019). In male mice treated with 17α-estradiol, the higher body weight is associated with heavier skeletal muscles and larger muscle fibers compared with untreated mice during aging, and associated with improved grip strength and rotarod capacity at 25 months. Sex-specific responses to 17α-estradiol appear to be regulated by gonadal hormones as castrated males have heavier quadriceps than intact males at 25 months, but do not respond to 17α-estradiol. Importantly, treatment started at late-life (at 16 months of age) show similar benefits, suggesting that 17α-estradiol may be able to improve aspects of late-life function even when started after middle age.

Proteostasis: NO BENEFIT BASED ON A RODENT STUDY
In older male mice, treatment with 17α-estradiol (14.4 ppm in diet) for 5 weeks did not increase the contribution of protein synthesis to proteostatic processes, in contrast to what is observed in caloric restriction models (Miller et al., 2020). Thus the mechanism through which 17α-estradiol exerts lifespan extension is not through the same proteostatic mechanisms seen with caloric restriction.

Safety: Based on one safety trial in postmenopausal women and several trials of topical formulations in people with hair loss, side effects were rare and mild. No safety data exists for long-term oral treatment in humans.

Types of evidence:

- 1 phase I double-blind randomized controlled trial testing safety in postmenopausal women
- 1 double-blind randomized controlled trial in people with alopecia (in German; not accessible)
- 1 single-blind clinical trial in female pattern hair loss
- 1 open-label, phase 4 study in women with female pattern hair loss
- 1 open-label noncomparative retrospective study in female pattern hair loss
- 2 mouse lifespan studies

Clinical studies: In a small phase I safety study of 8 healthy postmenopausal women, single rising oral doses of 17α-estradiol (MX-4509; 50, 100, and 200 µg, 7 days in between doses) were well-tolerated and no adverse events were reported (Dykens et al., 2005). All biochemistry, hematology, urinalysis, vital signs, and ECG measurements were within normal ranges. There was also no detectable conversion of 17α-estradiol to 17β-estradiol, the latter of which more strongly activates ERα, which in turn can promote tumorigenesis in the breast and reproductive organs (Higa and Fell, 2013).

Topical applications: Topical application has also been tested for hair loss. In a double-blind randomized controlled study in 51 people with hair loss, topical application of 0.025% 17α-estradiol for 6 months did not cause any side effects, though the paper was in German and only the abstract was accessible (Orfanos and Vogels, 1980). In a more recent open-label non-comparative clinical trial in 53 women with female pattern hair loss, daily topical application of 0.025% 17α-estradiol (Ell-Cranell® alpha 0.025%) was well-tolerated for 8 months (Kim et al., 2012). Side effects included an itching sensation and irritation at the application site—no systemic reactions were observed.

In an open-label noncomparative retrospective study of 34 women with female pattern hair loss, treatment with topical 0.025% 17α-estradiol and 3% minoxidil (vasodilator used for hypertension and hair loss) once daily for more than 6 months resulted in only a minority of patients complaining about mild discomfort during the study (Choe et al., 2017). No adverse events beside irritation/pruritus were causes for study withdrawal.

In a single-blind clinical trial of 119 postmenopausal women with female pattern hair loss, treatment with topical 0.05% 17α-estradiol and 0.5% finasteride (5-α reductase inhibitor used for hair loss and urinary retention) was tested for efficacy in hair restoration (Rossi et al., 2020). However, adverse events were not evaluated or discussed in this study.

Preclinical studies: In male mice, 17α-estradiol (14.4 mg/kg/day) does not appear to be feminizing (Stout et al., 2016). It did not significantly alter gonadal or seminiferous tubule mass, though means were lower in the 17α-treated compared to controls. No group differences were found in testosterone and 17β-estradiol levels. However, this study was not part of the ITP study and may have not had sufficient power to detect changes in male reproductive organs or hormone levels.

In female ovariectomized mice, 14.4 mg/kg/day of 17α-estradiol increased uterine weight to levels comparable to those of surgically-naïve controls (Strong et al., 2016). Compared to 17β-estradiol, 17α-estradiol is a significantly weaker agonist to the classical estrogen receptors (ERα and ERβ), but at sufficient high concentrations it likely activates these receptors and modulate reproductive and other estrogen receptor-mediated functions in both males and females. The finding on uterine weight raises concerns for potential uterotrophic effects such as endometriosis and cancer. The dose that generates the best anti-aging benefit without initiating the feminizing/tumorigenic effects is currently not known. It is worth noting that most deaths in the mice used in the NIA ITP studies are attributable to some form of neoplasia (abnormal growth). More research on the role of 17α-estradiol on oncogenesis is needed.

α-DHED, a bioprecursor prodrug that produces 17α-estradiol selectively in the brain, is under development and has shown selective increase in 17α-estradiol levels in the brain without increasing peripheral levels (Prokai-Tatrai et al., 2018). In mice, 17α-estradiol administration produces a significant increase in uterine weight (46 ± 8 mg) even at 30 µg/kg body weight dose that was insufficient to trigger CNS/antidepressant-like response. In contrast, α-DHED treatment (300 µg/kg body weight, once daily) for 5 consecutive days did not increase uterine weights (19 ± 3 mg) compared to control mice (17 ± 4 mg).

Drug interactions: Drug interactions are unknown and only a few studies have been carried out in humans.

Sources and dosing: The hormone is not on the market in the US. In the phase I safety trial in postmenopausal women, single rising doses of 50, 100, and 200 µg were used and well-tolerated (Dykens et al., 2005). For treatment of hair loss, topical formulations with 0.025% 17α-estradiol (Ell-Cranell® alpha 0.025%) improved hair counts and diameter and side effects were mild (Orfanos and Vogels, 1980; Kim et al., 2012). In mice, doses of 4.8 mg/kg and 14.4 mg/kg have been used, with the latter producing more consistent results in increasing lifespan in males (Harrison et al., 2014; Stout et al., 2016). However, the higher dose also increased uterine weight in females (Strong et al., 2016). The human equivalent doses based on body surface area are 0.62 mg/kg and 1.87 mg/kg, respectively.

Research underway: No clinical trials are under way. NIH is currently funding Dr. Michael Stout at the University of Oklahoma Health Sciences Center for preclinical work on the effects of 17α-estradiol on diabetes and inflammatory disorders (K99AG051661).

10β,17α-dihydroxyestra-1,4-dien-3-one (α-DHED), a bioprecursor prodrug that produces 17α-estradiol selectively in the brain, is under development (Prokai-Tatrai et al., 2018). This prodrug, which may be ideal for central nervous system indications, has been studied in preclinical models but have not been tested in humans to date.

Search terms:

Pubmed, Google: 17α-estradiol, 17αE2, alphatradiol

- + dementia, + cognitive, + ApoE4, + Alzheimer's, + aging, + safety, + inflammation, + alopecia, + lifespan

Clinicaltrials.gov, NIHRePORT: 17α-estradiol, 17αE2, alphatradiol

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If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact INFO@alzdiscovery.org. To view our official ratings, visit Cognitive Vitality's Rating page.