

Abstract

# CNS-Selective Estrogen Therapy <sup>†</sup>

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**Abstract:** 17 $\beta$ -Estradiol (E2), the main human estrogen, has been known to exert multiple actions throughout the body, including in the central nervous system (CNS). In particular, it has been shown that E2 is gender-independently needed for brain and eye health. Lack of E2 due to normal aging and/or pathological processes leads to neurological and psychiatric diseases as well as accelerated neurodegeneration. Current estrogen replacement therapies, however, cannot be used as therapeutic interventions to treat these maladies due to a profound, unwanted hormonal exposure to the rest of the body. In this presentation, we show that the small-molecule bioprecursor prodrug 10 $\beta$ ,17 $\beta$ -dihydroxyestra-1,4-dien-3-one (DHED) produces E2 only in the CNS but remains inert in the rest of the body, both upon chronic systemic and topical administrations, thereby avoiding the detrimental side-effects of the hormone, such as stimulation of the uterus and tumor growth. The highly localized production of E2 in the CNS will be shown through a series of bioanalytical assays and efficacy studies using animal models of estrogen-responsive maladies pertaining to the brain and the retina. Owing to DHED's significantly more favorable physicochemical properties than the highly lipophilic parent E2 for transport through biological membranes such as the blood-brain barrier or the cornea, a highly effective E2 therapy can be achieved in rodents upon prodrug administration, which further enhances therapeutic safety. Altogether, our patented DHED approach shows unprecedented selectivity to deliver E2 into the CNS and, thus, promises a high translation value in terms of efficacious and safe treatment against neurodegeneration as well as neurological and psychiatric symptoms arising from estrogen deficiency.

**Keywords:** 17 $\beta$ -estradiol (E2); bioprecursor prodrug; 10 $\beta$ ,17 $\beta$ -dihydroxyestra-1,4-dien-3-one (DHED); CNS-selective prodrug

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**Conflicts of Interest:** The authors are inventors in the patents covering the use of DHED as a CNS-selective bioprecursor prodrug of E2 and are co-founders of AgyPharma LLC with equity in the company that licensed the patents.



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