Not All Androgen Deprivation Therapies Are Created Equal: Leuprolide and the Decreased Risk of Developing Alzheimer's Disease

Nead et al¹ report that androgen deprivation therapy (ADT) used for the treatment of prostate cancer increases the risk of developing Alzheimer's disease (AD). Whereas testosterone signaling likely plays a major role in maintaining normal brain health, other hormones of the hypothalamic-pituitary-gonadal (HPG) axis may be just as important if not more so.² The fact that different ADTs operate via different mechanisms, with different effects on HPG hormones, seems not to have been taken into account by Nead et al¹; this likely explains why the conclusion is inconsistent with previous studies.

In particular, the findings of Nead et al¹ are in direct opposition to those from a study by D'Amico et al³ that was not cited. The study by D'Amico et al³ compared risk of death from AD in men with prostate cancer who underwent brachytherapy with (n = 1,700) versus without (n = 4,947) a gonadotropin-releasing hormone (GnRH) agonist. Risk of death as a result of AD was significantly decreased in those who received a GnRH agonist (adjusted hazard ratio, 0.45 [95% CI, 0.25 to 0.83]; *P* = .01).

The most likely cause for these conflicting results is that the article by Nead et al¹ considers all ADTs to be equivalent. ADT refers to a large number of different therapies with the overall end effect of suppression of testosterone signaling. For example, the 29 ADT medications queried by the authors in the generation of their data set have different mechanisms of action and heterogeneous effects on other HPG axis hormones. The primary HPG axis hormones affected include GnRH, luteinizing hormone (LH), follicle-stimulating hormone (FSH), estrogen, progesterone, follistatin, inhibins, and activins. For instance, GnRH agonists suppress circulating levels of LH, FSH, and sex steroids.⁴ Flutamide causes an increase in all of these hormones.⁵ Bicalutamide increases LH and FSH, but leaves testosterone levels unchanged.⁶ Ketoconazole has been shown to stimulate FSH and LH production and suppress estradiol production, but leave levels of prolactin, testosterone, and progesterone unchanged.⁷

Unfortunately, the risk of AD was not analyzed according to the type of ADT an individual received. Reanalysis of these results might be expected to demonstrate a decreased risk of AD with ADTs that decrease LH and an even greater risk of AD with ADTs that decrease testosterone but increase LH.

Although we agree with Nead et al¹ and others² that, overall, lower testosterone signaling may be associated with increased risk of neurodegeneration, it is critically important to understand that

other hormones also affect risk of AD. In particular, there is a large body of preclinical research that indicates that LH promotes AD pathology⁸ and that treatments that lower LH, including GnRH agonists such as leuprolide acetate, decrease AD pathology (reviewed in Bowen et al⁸). Leuprolide acetate is an ADT proven to be effective against prostate cancer that may also slow progression of AD in humans.^{9,10}

It is important that readers of the report by Nead et al¹ not be left with the impression that men faced with prostate cancer must choose between risk of cancer and risk of AD. Leuprolide acetate and other LH-lowering therapies may be effective against both devastating diseases.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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