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What are the Possible Implications for Androgen Replacement Therapy on Central Nervous System Function in Aging Men?

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Aging and Steroid Hormones

Hypogonadism is a clinical condition depicted by low androgen levels and associated with low muscle mass and strength, decreased ratio of lean body mass to adipose tissue, osteoporosis, decreased libido, decreased hematocrit, impaired cognition, and mood disorders [1]. It has been well established that aging is associated with decreased testosterone levels in males, and by 80 years of age, 40% of men have serum testosterone levels within the hypogonadal range [2]. Hypogonadism in aging males is often called andropause or androgen deficiency of the aging male (ADAM) [3]. However, assessment of andropause in aging males is difficult due to several factors, such as varying methods of testosterone measurements (total testosterone, bioactive testosterone not bound to sex hormone-binding globulin (SHBG), and free testosterone not bound to SHBG or albumin proteins) [4]. Further complicating diagnoses is that SHBG levels increase during aging, resulting in decreased bioactive and free testosterone levels [4]. Since andropause can affect the quality of life for aging men and the elderly population is predicted to double by 2025, investigation of andropause becomes imperative [5].

Androgen Replacement Therapy

In aging males, low testosterone levels are predictive of future development of mobility limitations and frailty [6,7]. Androgen replacement therapy (ART) in elderly male subjects has been considered as a restorative/protective treatment modality against various disorders associated with aging [8-11]. ART is currently only indicated by the FDA for males that have been diagnosed with hypogonadism. The Endocrine Society's clinical practical guideline for ART in adult men with testosterone deficiency has defined hypogonadism in males as "a clinical syndrome that results from failure of the testis to produce physiological levels of testosterone and a normal number of spermatozoa due to a disruption of one or more levels of the hypothalamic-pituitary-gonadal (HPG) axis" [12]. Primary hypogonadism is characterized by high luteinizing hormone and follicle stimulating hormone levels in response to diminished HPG feedback, while secondary hypogonadism is characterized by low testosterone levels associated with low or normal luteinizing hormone or follicle stimulating hormone levels [13].

Medications that have been approved by FDA to treat hypogonadism include several Schedule III controlled substances, such as testosterone injections, transdermal testosterone patches/gels, and oral testosterone formulations [14]. In the United States, alone, prescription sales of testosterone products have increased more than 500 percent since 1993 [15]. However, the data obtained to date that describe the protective effects of ART in elderly men have been equivocal, in contrast to findings in younger hypogonadal men [16,17]. Further, concern about the efficacy of ART in aging men prompted the National Institute of Aging and the National Cancer Institute to request that the Institute of Medicine conduct a 12-month study to evaluate the current understanding of the potential benefits and adverse effects of ART. A major theme in the analysis and recommendation was that additional work must be done before clear decisions can be made about the future of ART [18].

Androgen Replacement Therapy and the Central Nervous System

Our understanding of steroid hormone biology during aging is incomplete and current data about hypogonadism in the aging male population has been equivocal on the effects of testosterone on various endpoints, in contrast to findings in younger hypogonadal men [16,17]. The current contraindications for ART in aged males consist of obstructive benign prostatic hyperplasia, obstructive pulmonary disease, heavy smokers, clinical prostatic carcinoma, polycythemia, mammary carcinoma, prolactinoma, and dyslipidemia [19]. Interestingly, the effects of ART on the central nervous system have not been thoroughly examined, even though aging and male gender are two of the clinical risk factors for neurodegenerative disorders, such as Parkinson's disease [20,21]. A possible explanation for the inconsistent reports in aged men may be that ART has both positive and negative therapeutic effects, depending on the oxidative stress load. Oxidative stress has been shown to contribute to both aging [22-24] and neurodegeneration [20,21,25,26]. Studies have determined that oxidative stress may mediate the apoptotic loss of dopamine neurons in neurodegenerative diseases, such as Parkinson's disease [27-29]. Further complicating the issue of ART and aging, androgens can also induce oxidative stress in dopamine neurons [30]. The effects of androgens on neurodegeneration are controversial. Animal studies suggest that the lack of androgens contribute to oxidative stress and neurodegeneration [31-33], conversely other studies suggest that androgens can mediate oxidative stress and neurodegeneration [34-37]. Available data indicate that there is an existing gap in our understanding of the efficacy and contraindications of ART in the elderly male population with regard to aging associated oxidative stress burden and subsequent neurodegeneration. Therefore, it is extremely important for the scientific community to develop agreement about ART safety in aging males, while taking into consideration possible ART-induced effects on the central nervous system along with the current contraindications associated with ART.

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