Australian Government
Repatriation Medical Authority

REPATRIATION MEDICAL AUTHORITY

STATEMENT OF REASONS

S196B(9) *VETERANS' ENTITLEMENTS ACT 1986*

DECISION NOT TO AMEND THE CURRENT STATEMENTS OF PRINCIPLES CONCERNING ALZHEIMER-TYPE DEMENTIA FOLLOWING A REVIEW

Statements of Principles Instrument Nos. 22 & 23 of 2010, as amended

PART I INTRODUCTION

1. The Repatriation Medical Authority (the Authority) has decided not to amend the Statements of Principles concerning Alzheimer-type dementia Instrument Nos. 22 & 23 of 2010, as amended, under subsection 196B(9) of the *Veterans' Entitlements Act 1986* (the Act), following an investigation which was notified in the *Commonwealth of Australia Gazette* on 19 October 2016.

2. The Authority concluded that there is insufficient new sound medical-scientific evidence to justify an amendment to Statements of Principles Instrument Nos. 22 & 23 of 2010, as amended, already determined in respect of Alzheimer-type dementia.

PART II BACKGROUND TO THE INVESTIGATION

3. A request dated 3 August 2016 was received from a person acting on behalf of a veteran's widow seeking a review of the Statements of Principles concerning Alzheimer-type dementia with respect to the inclusion of a new factor concerning androgen deprivation therapy.

4. On 12 October 2016, the Authority, under subsection 196B(7A) of the Act, decided to review the contents of the Statements of Principles Instrument Nos. 22 & 23 of 2010, as amended, to find out if there was new information in respect of "androgen deprivation therapy " as a factor in Alzheimer-type dementia.

5. In support of the review, the Authority considered the following:

   - A published peer-reviewed article -

     Nead KT, Gaskin G, Chester C, Swisher-McClure S, Dudley JT, Leeper NJ, Shah NH. (2016) Androgen Deprivation Therapy and Future Alzheimer's Disease Risk. J Clin Oncol. Feb 20;34(6):566-71.

   - A news item from the Wall Street Journal referring to the above article.

6. The investigation notice was signed by the Chairperson of the Authority on 14 October 2016 and was gazetted in accordance with section 196G of the Act in the *Commonwealth of Australia Gazette* on 19 October 2016. Submissions were invited from persons and organisations wishing to make a submission by 2 December 2016.

7. Statements of Principles Instrument Nos. 22 & 23 of 2010, as amended, concerning Alzheimer-type dementia do not have any factors relating to "androgen deprivation therapy".

PART III SUBMISSIONS RECEIVED BY THE AUTHORITY PURSUANT TO SECTION 196F

8. Following notification of its investigation, the Authority did not receive any information from persons eligible to make submissions pursuant to section 196F of the Act.

PART IV EVIDENCE/INFORMATION AVAILABLE TO THE REPATRIATION MEDICAL AUTHORITY

9. The following information was available to the Authority.

   9.1. The information held by the Authority and obtained during its previous considerations leading to the determination of Statements of Principles concerning Alzheimer-type dementia, Instrument Nos. 22 & 23 of 2010, as amended.

   9.2. Literature searches were conducted using the Ovid search engine from 1996 to December Week 1 2016, limited to English language. The search terms were: Exp Alzheimer's disease.mp. or exp Alzheimer Disease/ AND Antineoplastic Agents, Hormonal/ or androgen deprivation therapy.mp. or Orchiectomy/ or Androgen Antagonists/. The above search was supplemented by PubMed and internet searches, manual searches of reference lists and extracts from relevant sections of textbooks.

   9.3. Medical or scientific publications as set out in the bibliography attached hereto.

10. A briefing paper concerning Alzheimer-type dementia prepared for presentation to the Authority by a Medical Researcher of the Secretariat.

PART V SOUND MEDICAL-SCIENTIFIC EVIDENCE

11. The Statements of Principles are determined on the basis of the available "sound medical-scientific evidence" as defined in section 5AB(2) of the Act which states:

"*Information about a particular kind of injury, disease or death is taken to be* ***sound medical-scientific evidence*** *if:*

(a) the information:
   (i) is consistent with material relating to medical science that has been published in a medical or scientific publication and has been, in the opinion of the Repatriation Medical Authority, subjected to a peer review process; or
   (ii) in accordance with generally accepted medical practice, would serve as the basis for the diagnosis and management of a medical condition; and

(b) in the case of information about how that kind of injury, disease or death may be caused - meets the applicable criteria for assessing causation currently applied in the field of epidemiology."

PART VI REASONS FOR THE DECISION

12. There is concern that androgen deprivation therapy (ADT) may cause impairment of cognitive function and increase the risk of developing dementia, although the role of sex hormones in the pathogenesis of Alzheimer's disease is controversial.

13. Androgen deprivation might affect cognitive function by impairing neuron growth and axonal regeneration, increasing the accumulation of β-amyloid protein and adversely affecting cardiometabolic risk factors (Nead et al 2016a). ADT has been associated with increased risk of diabetes mellitus (Bosco et al 2015). It has also been suggested that higher levels of luteinising hormone caused by age or therapy related-reduction in testosterone levels might affect the memory processing areas in the hippocampus, which contains the highest density of LH receptors in the brain (Bowen et al 2016).

14. Conversely, cognitive decline and/or dementia could lead directly or indirectly to changes in androgen status (Hsu et al 2015). Indirect effects of dementia on androgen status could occur via reduced physical function in older men and women with dementia, which is associated with a lowering of androgen status as partially reflected by serum testosterone in older men. Cognitive decline may also invoke other nonspecific adaptive responses that impair hypothalamic regulation of reproductive function and androgen status.

15. Studies have examined the relationship between androgens and cognitive function or dementia in several different ways, as summarised below:

Testosterone and cognitive function

16. In 6 longitudinal and 14 cross-sectional studies of endogenous testosterone levels, results were mixed, with positive, negative, null and curvilinear associations against different cognitive measures (Hua et al 2016). The findings of one cohort study (Hsu et al 2015) raise the possibility that decline in androgen status may be the consequence rather than the cause of cognitive decline, consistent with the absence of significant cognitive decline in life-long hypogonadism as well as randomized placebo-controlled trials that find little or no benefits of testosterone treatment on cognitive function in older men. None of the baseline reproductive hormones predicted cognitive decline in men without dementia over 5 years but the change in serum hormones over time was associated with cognitive decline.

Testosterone and risk of Alzheimer-type dementia

17. A meta-analysis of plasma total testosterone, oestradiol, and sex hormone-binding globulin (SHBG) levels among patients with Alzheimer's disease found significant elevations in SHBG, but no difference in testosterone levels between people with Alzheimer's disease and matched controls (Xu et al 2016). Elevated SHBG reduces bioavailable testosterone, but the significance of this in relation to Alzheimer's disease risk is uncertain. Another meta-analysis of 7 prospective cohort studies (Lv et al 2016) found that low plasma testosterone level was significantly associated with an increased risk of Alzheimer's disease in elderly men (RR 1.48, 95% CI 1.12-1.96), but there was inconsistent and incomplete control for confounding across different studies. If low testosterone is causally related to a reduction in cognitive function then replacement should reduce the risk.

Testosterone replacement and cognitive function

18. A systematic review of randomised controlled trials found that, while there was some evidence that testosterone replacement may slow cognitive decline in eugonadal men, there are insufficient data to support the use of testosterone in men with low testosterone levels (Hua et al 2016). Since that review was published, a small trial of testosterone treatment in men with subjective memory complaint and low testosterone levels found improvements relative to baseline but not in relation to placebo (Wahjoepramono et al 2016). A larger trial found no effect of restoring physiological levels of testosterone on any test of cognitive function in men with normal cognitive function (Huang et al 2016).

ADT and cognitive function

19. A meta-analysis of 3 cross-sectional and 11 longitudinal studies found that patients treated with ADT performed worse than controls or their own baseline on visuomotor tasks. No significant effect sizes were observed for the other six cognitive domains (McGinty et al 2014). A prospective cohort study published since this meta-analysis (Gonzalez et al 2015) found impaired overall cognitive performance over time compared with controls, but the only significant domain was in one of three tests of executive function. Visuomotor function and working memory were not assessed in this study.

ADT and risk of Alzheimer-type dementia

20. Three cohort studies examined the association between ADT and risk of Alzheimer-type dementia. In a retrospective US cohort study using administrative data (Nead et al 2016a) there was a significant 66% to 88% increase in risk of Alzheimer-type dementia in patients who had used ADT. In a sub-analysis of these data, Nead et al (2016b) found a significant positive association between Alzheimer-type dementia in those who used ADT and who were 70 years or older, with a dose response effect. A similar increase was observed in the association between ADT use and all forms of dementia combined (Nead et al 2016c).

21. In another retrospective cohort study using a Taiwanese population-based database (Chung et al 2016), there was an elevated but non-significant association between ADT use and risk of Alzheimer-type dementia.

22. A third retrospective cohort study found that there was a significant reduction in the risk of death from Alzheimer's disease in men who were treated with a luteinising hormone (LH) agonist for a median of 4.0 months as compared with those who were not (D'Amico et al 2010).

Limitations of the available data

23. An important consideration in assessing the association between Alzheimer-type dementia and ADT is confounding by indication. Individuals may be more likely to receive radiation therapy and ADT if they are poor surgical candidates with a high number of comorbidities. Cardiometabolic risk factors are also risk factors for Alzheimer's disease. In the study by Nead et al (2016a), ADT users were about 4 years older than non-users, and in the short follow up period of 2.7 years non-users might not have had time to develop dementia. D'Amico et al (2010) found that patients given ADT were significantly older (by almost 2 years) and tended to have higher stage disease. ADT necessitates the use of more outpatient visits, which may increase the opportunity to be diagnosed with Alzheimer-type dementia.

24. Another problem with the available data is that different forms of ADT cause lowering of testosterone by different mechanisms, and in particular may increase or decrease levels of gonadotropins. It has been suggested that high levels of LH rather than low levels of testosterone may be the mechanism for cognitive effects. In that case LH agonists (which eventually lower LH after an initial surge) or LH antagonists might actually improve cognitive function. This was one possible explanation of the finding of a reduction in death from Alzheimer-type dementia in men treated with LH agonists in the study by D'Amico et al (2010). A study in mice found that lowering LH levels caused

a reduction in beta-amyloid levels in the brain (Bowen et al 2016). There is animal data showing that the use of an LHRH agonist to markedly lower serum LH levels leads to improved hippocampally related cognitive performance (cited in D'Amico et al 2010).

25. Hua et al (2016) point out that there are inherent difficulties in studying testosterone and cognition in that the underlying physiology is both complex and dynamic, involving the entire hypothalamic-pituitary-adrenal-gonadal axis as well as multiple additional internal and external factors. The different effects of different forms of ADT on the hypothalamic-pituitary-adrenal-gonadal axis only add to the complexity.

26. Most commentators did not feel that the study by Nead et al was sufficient to warrant a change in practice, given the benefits of the treatment on improving survival in patients with prostate cancer (Taneja et al 2016, Penson 2016, McGinty 2016, Froehner and Wirth 2016). Nead et al agree that further studies are needed to confirm their findings.

Conclusions

27. Postulated mechanisms for the effects of ADT on cognitive function include potentially adverse effects from beta-amyloid deposition and metabolic changes and potentially positive effects from decreases in LH levels leading to improved hippocampally related cognitive performance.

28. Because of the limitations in the one study that did show a significant association between ADT and Alzheimer-type dementia, a lack of a significant positive association between ADT and Alzheimer-type dementia in two other studies, the possibility of reverse effects of cognitive decline on androgen levels, uncertainty about which form of ADT is relevant and the lack of a clear benefit of testosterone replacement on cognitive function in men with low testosterone levels, it appears that the effects of ADT on risk of Alzheimer-type dementia are still uncertain at present.

PART VII DECISION

29. At its meeting on 7 February 2017 the Authority decided not to amend the Statements of Principles in respect of Alzheimer-type dementia for the purposes of subsections 196B(2), (3) and (8) of the Act as the Authority concluded, for the reasons set out above, that there is insufficient new sound medical-scientific evidence to justify an amendment to the Statements of Principles already determined in respect of Alzheimer-type dementia.

Professor Nicholas Saunders AO
Chairperson
Repatriation Medical Authority

24 February 2017

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