



Editorial

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Treatment of Prostate Disease and Cognitive Problems

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Benign prostatic hyperplasia (BPH) is one of the most common diseases in older men, affecting more than 70% of men over 70 years of age, and prostate cancer (PC) is the most common cancer in men in the United Kingdom and United States.

Clinicians use α_1 -adrenergic antagonists to manage lower urinary tract symptoms (LUTS) associated with BPH in older men. These drugs are often the first choice of treatment because they are effective, well tolerated, and reasonably priced. Additionally, androgen deprivation therapy (ADT) is a mainstay of PC treatment and has been shown in randomized trials to improve overall survival when used with radiation for intermediate- and high-risk localized disease, as well as locally advanced and node-positive disease [1].

Recently, some reports have suggested that these medications, which are widely used to treat BPH and PC, may adversely affect patients' cognitive function.

Duan et al. [2] utilized Medicare claims data from 2006 to 2012 to conduct a cohort study among men aged ≥ 65 years who had been diagnosed with BPH. Their analysis showed that compared with the no-BPH-medication cohort, the tamsulosin cohort showed a significantly increased risk of dementia, with 31.3 vs. 25.9 cases/1,000 person-years (hazard ratio, 1.17; 95% confidence interval, 1.14–1.21) [3].

Unsurprisingly, counterarguments have been made against this study. Several studies have shown that tamsulosin has a limited ability to pass through the blood-brain barrier. Therefore, some have argued that it remains unclear how a drug with minimal penetration into the brain could promote the occurrence of dementia [4].

Adverse effects of ADT include decreases in bone mineral den-

sity, metabolic changes such as weight gain, decreased muscle mass, and increased insulin resistance. Some epidemiological studies have shown ADT to be linked with an increased risk of diabetes and cardiovascular disease [1]. Studies have shown discordant results regarding the precise impact of ADT on cognition.

Green et al. [5] randomized 82 men to a luteinizing hormone-releasing hormone agonist, cyproterone acetate, or observation. They found that half the men assigned to therapy had a clinically significant decline in one or more cognitive tests at 6 months compared with none of the men in the observation group. However, these results were not confirmed in the largest prospective study of this issue, which was conducted by Alibhai et al. [6]. They enrolled 241 men with PC treated with ADT, PC and no ADT, or no PC. After adjusting for age and education, the study found no consistent effect of ADT on cognitive function.

In the present issue of the *International Neurourology Journal* (INJ), Shin et al. [7] report that long-term surgical and chemical castration causes memory function to deteriorate through down-regulation of the protein kinase A (PKA)/cyclic adenosine monophosphate response element-binding protein (CREB)/brain-derived neurotrophic factor (BDNF) and c-Raf/mitogen-activated protein kinases-extracellular signal-regulated kinases (MEK)/extracellular signal-regulated kinases (ERK) pathway in the hippocampus. The hippocampus is a target of androgen action, and testosterone improves hippocampal neurogenesis through an androgen-dependent mechanism. Down-regulation of the PKA/CREB/BDNF and c-Raf/MEK/ERK pathways may result in decreased neurogenesis, and this result may provide an important clue regarding the cognitive decline associated with androgen deprivation.



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In another study published in this issue of INJ, Yamatoto et al. [8] show the possibility that α_1 -adrenergic antagonists may exert an effect on the spinal cord level beyond the bladder, prostate, and urethra. They investigated naftopidil, an α_1 -adrenergic antagonist that has 3 times greater affinity for the α_{1D} -adrenergic receptor subtype than for the α_{1A} subtype, and found that with anesthesia, micturition intervals were moderately shortened by emotional stress and clearly improved by naftopidil. Therefore, naftopidil appears to act at the spinal level, in addition to its other effects.

Given the high prevalence of BPH, LUTS, and cognitive impairment among elderly men, any potential impact of α_1 -adrenergic antagonists on cognitive function is a clinically relevant health issue. Although ADT can improve survival for men in certain settings, ADT also has a variety of potential harms to PC patients. Therefore, we should continue to investigate the effects of these drugs on the central nervous system, including the spinal cord, in addition to their effects on the target organ.

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