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Marijuana, Alcohol, and ED: Correlations with LUTS/BPH

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Abstract

Purpose of Review—Benign prostatic hyperplasia (BPH) and lower urinary tract symptoms (LUTS) is a disease complex with enormous societal burden and yet the pathogenesis of LUTS/BPH is poorly understood. We set out to review the literature on the relationship between depression, marijuana usage, and erectile dysfunction (ED) to LUTS/BPH.

Recent Findings—LUTS/BPH has independent associations with depression as well as with ED. In each case, the causality and mechanistic relationship is unknown. The impact of marijuana, as it increasingly pervades the general population, on the disease complex of LUTS/BPH is not well studied but recent results support short-term benefit and long-term caution.

Summary—Depression, a form of central nervous dysfunction, and ED, which is likely mediated via endothelial dysfunction, are independently associated with LUTS/BPH. The presence of cannabinoid receptors in urologic organs, coupled with recent population studies, supports a modulatory effect of marijuana on voiding although an enormous knowledge gap remains.

Keywords

BPH; Voiding; LUTS; Prostate; Marijuana; ED

Introduction

Benign prostatic hyperplasia (BPH) and BPH-associated lower urinary tract symptoms (LUTS) have a significant impact on men's health. Globally, BPH carries the highest health burden of any urologic disorder, malignant or benign, and is poised to rise even more rapidly [1]. As the population ages and the societal burden of LUTS/BPH increases, better

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understanding of its underlying causes and associated disease processes becomes more critical. LUTS/BPH has multiple causative factors and many epidemiologic correlates, but an effective and unifying understanding of this heterogeneous disease has proven elusive.

Specific associations have been investigated in hopes of better understanding how to treat and avoid progression of BPH and LUTS. Metabolic syndrome (MetS) has been linked with the disease process of LUTS/BPH, but evidence has been variable and inconclusive [2•]. Hypertension (HTN), type 2 diabetes (DM), obesity, physical inactivity [3, 4], autonomic nervous system overactivity [5], prostate growth rates, and failure of senescence [6, 7] have all been found to contribute to or correlate with LUTS/BPH. Other community surveys of erectile dysfunction (ED) found that prostatitis and incontinence are strongly associated with LUTS/BPH [8], and a subsequent meta-analysis verified deep interrelationship between these two diseases of the aging male. Implicating central nervous system involvement in the process, depression has been linked with both LUTS and BPH although causality is unknown [9–12]. Furthermore, recent studies have shown a relationship between marijuana usage and LUTS/BPH that suggest short-term improvement in voiding but raise concerns about long-term usage [13–17]. However, we are unaware of any data showing impact on urinary function related to alcohol usage. We set out to review the latest literature on the relationship between LUTS/BPH, and these comorbid conditions and coexisting habits.

Marijuana Use and LUTS

Marijuana is a product derived from the cannabis plant, a flowering member of the family *Cannabaceae*. The genus is thought to be indigenous to central Asia. Medicinal uses for marijuana date back 5000 years across many cultures for a variety of medical problems. The active ingredients of marijuana include tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is a psychoactive compound which can induce euphoria, relaxation, altered perception of time, increased appetite, and heightened sensory perception [18]. CBD is a non-psychoactive substance that is hypothesized to have an effect on anxiety, cognition, movement disorders, and pain [19]. Suggestive of pharmacologic effect, usage for myriad processes has been reported in the modern medical literature for hundreds of years [20].

THC, the primary identified active agent in marijuana, mediates effect on target tissue via two primary receptors: CB-1 and CB-2. This identification of a direct effect of cannabinoids on the bladder, and the identification of the widespread cannabinoid receptor (CB-1) as a mechanism for the mediation of that effect, has led to studies, primarily in murine models. The second receptor, CB-2, shares 44% homology with CB-1 and is more limited in distribution, being mostly found in brain and testes [21].

Translational Studies of Cannabinoid Effects on Bladder and Voiding

Cannabinoids have been observed to modulate bladder function in animal models including an increase in voided volume, voiding pressure, and prolonged intermicturition intervals [22••]. Direct arterial injection of CB agonist also decreased bladder voiding threshold, both at baseline and in response to irritants [23]. This effect was ameliorated by competitive antagonists of the receptor. Intravesical instillation of synthetic cannabinoids also had an

effect on bladder response pointing towards the involvement of CB-1 receptors when compared to the CB-2, with CB-1 appearing to be the primary mediator of voiding effects [24]. In a separate murine model of acrolein-induced cystitis, cannabinoids were found to significantly counteract the irritative effects of the chemical, suggesting a potential role for bladder pain management in humans [25, 26]. Overall, THC and synthetic cannabinoid agonists of the CB-1 and to a lesser extent CB-2 receptor appear to have generally beneficial short-term effects on voiding in animal models. Long-term effects and chronic adaptation are still mostly unknown.

Effects of Marijuana on Human Voiding

Human voiding response to cannabinoids has not been much studied, although an identifiable effect appears to exist. Cannabis usage induced intriguing responses in bladder and urine proteomics: increases in immune response pathways, and carbohydrate-related mechanisms, among others [27]. Two cross-sectional population studies have found a statistically significant association between marijuana usage and the presence of LUTS. First, 3037 men aged 20–59 and completing the National Health and Nutrition Examination Survey from 2005 to 2008 found that self-reported marijuana users experienced less LUTS [28•]. More recently, it was observed that in a sample of 173,469 men (aged 45 or over), those who were identified as using cannabis were significantly more likely to receive treatment for LUTS/BPH than men who were not [29]. This “substance use-symptom” relationship between marijuana and LUTS/BPH was not present in the same group when assessed for the effects of alcohol consumption.

These two findings address separate end points: self-reported voiding dysfunction is different than the receipt of treatment for LUTS/BPH. Additionally, the age groups were somewhat different in these two groups, and it was not possible to control the NHANES data for age-related correlation of usage. This is important because the use of marijuana decreases substantially with age: 30% of adults in the 18–25 age group reported marijuana usage in the past year, but this rate drops to 3.4% of those who are 50–64 years old and 0.6% in adults over 65 [30]. It seems likely that adult marijuana users represent a somewhat distinct population subset, behaviorally, socially, or biologically. Perhaps, men who use marijuana, especially those that use into adult life and past the age of 45, find it therapeutic in the same fashion that leads general and younger users to report lower baseline urinary symptoms. Alternatively, continued consumption in later life may be a marker for long-term exposure and a high cumulative dose of cannabinoid, which in turn may represent a damaging effect. It is not possible to draw conclusions regarding effects of chronic exposure to marijuana from these data. Other substances of abuse and toxins can result in severe and direct urinary morbidity, such as ketamine [31], although this pharmacological agent is unrelated to THC and marijuana.

In multiple sclerosis (MS) patients, cannabinoids showed some beneficial effects on muscular spasticity and on urinary function in men and women, although results have varied between the studies and formulation of cannabinoid administration [32]. A survey of MS patients using marijuana found that over half of patients reported subjective improvement in urinary symptoms, and others confirmed improvement in urge and incontinence, thereby,

supporting self-selection for a perceived benefit of cannabinoids [14–17]. A controlled trial of cannabinoids and placebo in 24 patients with a variety of neurological symptoms, primarily from MS, showed a notable improvement in pain and other symptoms, including LUTS improvement in cannabinoid users.

Depression and LUTS

Depressive disorder is a common medical problem among older adult males. It has significant health-related quality of life implications including decreased functional status and increased mortality, and is a risk factor for the development of other chronic diseases [33]. Depression as a diagnosis is characterized by depressed mood and loss of interest in enjoyable facets of life and/or pleasure. The condition can manifest itself in a variety of ways both mentally and physically [34]. The prevalence of depression in adults is 7.7% in those age 20–39, 8.4% in those age 40–59, and 8.0% in those age 60 and over, according to the National Health and Nutrition Examination Survey (2013–2016). Clinical studies revealed a correlation between depression and the diagnosis of LUTS. A review of 547 men identified that the 22% who scored poorly on a geriatric depression scale were three times more likely to also have severe LUTS, as was defined by an IPSS score of > 20.[9] Similar observations have been made in patients from Australia and Korea [35–37], and a systematic review of nocturia also found strong correlation with depression [38]. Our group was able to identify the same association in an American sample of 173,649 men, with the diagnosis of depression carrying an odds ratio of 2.05 (95% CI 1.95, 2.16) for requiring LUTS/BPH therapy after multivariable controls [29]. The range of depression prevalence in patients with LUTS lies within 11.5–12.3% [39, 40]. The severity of LUTS directly correlates with increasing severity of depressive symptoms, as well as with higher odds of suicidal ideation in cross-sectional studies [41, 42]. Whether this is a centrally mediated effect or whether the depressive state is a consequence of other symptoms and organ dysfunction is still unknown.

The causality underlying the correlation between LUTS/BPH and depression is unknown. A Taiwanese prospective study determined a significantly higher rate of developing depression in patients diagnosed with BPH at the study onset in comparison with those who did not have a diagnosis of BPH (2.01% vs 1.01%, 1-year follow-up). The likelihood ratio of developing depression in those with BPH was 1.87 (95% CI = 1.63–2.16, $p < 0.001$) [43, 44]. There appears to be a temporal relationship between onset of BPH and subsequent development of depressive symptoms at 2 years, and our group's work on a large cross-sectional dataset found that depression carries a hazard ratio of 2.05 (95% CI: 1.95, 2.16, $p < 0.001$) which exceeds the ratio for diabetes, hypertension and obesity/metabolic syndrome. [29, 45] It has been suggested that the psychiatric effects of depression can manifest in worsened self-reported BPH symptoms as patient perspective is damaged [9]. Depression has also been shown to be an independent risk factor for progression of LUTS over time [9, 36, 41].

Whether the depressive state is a CNS-mediated effect, a consequence of other symptoms and organ pathology, or broad CNS dysfunction occurs in parallel to LUTS in the aging male is still unknown. Likely, a decline in organ function, for example, of the urinary

bladder, might be paralleled or enhanced by a decrease in the function of the central or peripheral nervous system.

Adding to the myriad of interrelated factors is the apparent interaction between depression and cannabis usage. A study of 14,000 twins from Australia as well as other groups has suggested a correlation between heavy marijuana usage and depression [46–49]. The exact relationship between the two entities is not completely established, but studies suggest that regular marijuana use in adolescents results in a decrease in size in certain regions of the brain (hippocampus, amygdala, prefrontal cortex) that are dense in endocannabinoid receptors [50]. Furthermore, early cannabis use was also associated with anhedonia and decreased serotonin levels in adults [51]. The underlying deficiency in the intrinsic endocannabinoid system may be involved in heightened risk of post-traumatic stress development and may be the cause of increased cannabis use [52]. The use of cannabinoids may also play a role in other behavioral diseases where the intrinsic endocannabinoid system appears to mediate neurochemical changes underlying the placebo effect [53]. Could a subset of individuals similarly discover that the addition of exogenous cannabinoid to their own internal milieu corrects other forms of bother? There is a complex interaction between cannabinoid use, depression, and LUTS and further studies will be needed to understand their effects on each other (Fig. 1).

Erectile Dysfunction

Erectile dysfunction (ED) and LUTS caused by BPH (LUTS/BPH) are highly common around the world. The prevalence of LUTS/BPH and ED in men increases with age, and both conditions have been found to coexist in many men [54]. Erectile dysfunction is defined as the inability to attain and maintain an erection sufficient for sexual intercourse at least 25% of the time [55]. The problem often develops gradually. The pathophysiology of ED in this group includes chronic ischemia, which leads to deterioration of cavernosal smooth muscle and the development of corporeal fibrosis [56]. Erectile dysfunction has diverse causality and includes side effects of some medications, iatrogenic nerve damage, and psychosocial causes: most but not all organic causes ultimately result in a failure of the vascular bed [57]. ED affects a large portion of the aging population, with the Massachusetts Male Aging Study finding that 52% of men aged 40–70 years develop some degree of ED. [58]

Although ED can be an isolated issue, often age and many of the same comorbidities that track with BPH also coexist with this disease. [59] Even a mild increase in LUTS/BPH severity parallels increases the incidence of ED, and also negatively affects quality of life in patients. A multinational prospective study of men describing sexual function and various comorbidities established that up to 90% of men had moderate to severe LUTS, the severity of which increased with age, while sexual dysfunction was reported at 82%. The level of sexual dysfunction directly correlated with the severity of LUTS [60]. Considering this data, LUTS itself is an independent risk factor for ED in addition to the commonly recognized risks factors such as age, diabetes, hypertension, and pelvic surgery [61]. Similarly, in a large cross-sectional analysis, the diagnosis of ED was associated with increased risk of being on a LUTS medication that persisted after controlling for other various comorbidities

(OR 1.80, 95% CI 1.67, 1.94, $p < 0.001$) [29]. Overall, these data provide evidence of a consistent and strong relationship between LUTS and ED. [62, 63]

Many theories have been postulated regarding the tissue- and organ-level etiology of ED. One of the suggestions includes an imbalance in the autonomic control of penile smooth muscle contractions and relaxations which may play an important role in both LUTS and ED. [64] Additionally, endothelial dysfunction associated with impaired endothelium-dependent vasodilation resulting from the decreased bioactivity of nitric oxide can link the two pathological conditions [65]. ED has been studied as a marker for systemic endothelial dysfunction, and has been shown to provide an early clue, for example, to the presence of occult cardiovascular disease [66]. This endothelial failure may define a physiological vulnerability of the bladder that is exaggerated during obstruction-mediated stress secondary to BPH, further accelerating the development of LUTS [67]. Furthermore, the prostate has nitric oxide receptors that modulate smooth muscle tone in the prostate and urethra, and likely are the mechanism by which phosphoesterase-5 inhibitors (PDE-5I) are effective in the management of LUTS [68].

Marijuana and Erectile/Sexual Function

The prevalence of cannabinoid use in the adolescent population seems to be stable despite growing legalization; however, usage rates in the adult population show growth along with a decrease in the perception of potential harm [69]. Given the historical paucity of research on marijuana usage, there is an increasing need to elucidate possible health repercussions. One of the observed negative impacts of marijuana use is the linkage of the use of marijuana with the development of ED. [70•] Considering that the causes of ED may be psychological, organic, or likely a mix of both, there are many questions of etiologies, cofactors, and comorbidities to consider. One possible mechanism is mediation via the endocannabinoid system and the binding of receptors in the paraventricular nucleus of the hypothalamus which regulates erectile function and sexual behavior of males [49, 71]. In addition, there could be a direct influence on the penis from the cannabis itself. Both animal and human studies reported a peripheral effect of cannabis on ED, specifically on corpus cavernosum where cannabinoid receptors are present [72, 73]. CB1 and CB2 receptors are located on NOS-containing nerves in primate and human corpus cavernosum tissues [72]. In murine models, CB1 receptor antagonist induced penile erection when injected into the paraventricular nucleus of male rats. [73] Considering the high correlation between ED and cannabis use, as well as potential harmful effects of marijuana on male sexual and general health, it is necessary to increase and improve the knowledge on this topic in order to achieve the best clinical and public health strategies [74].

Conclusion

In summary, we found a significant evidence of linkage between voiding function, sexual response, and the use of cannabinoids in the published literature. Based on the possible pathophysiological mechanisms of LUTS/BPH and ED as well as other common comorbidities observed in aging men with these conditions, further multidisciplinary studies are warranted [75•]. Men presenting with LUTS should be evaluated for sexual dysfunction

and ED, and those presenting with ED should be assessed for LUTS/BPH [68]. A thorough social history including illicit substance use is an important baseline set of data to register during patient evaluations.

Summary

Cumulative research in the domain of LUTS has shown an ever-more complex interaction between organs, systems, and environmental factors. LUTS/BPH is not purely consequent to processes occurring locally in the prostate, but involves processes and responses in the bladder, systemic microvascular bed, muscular system, and CNS. Establishing the relationships between comorbid conditions and their association with LUTS/BPH has proven useful to extend our understanding.

Depression

There is a clear association between LUTS/BPH and depression; however, the mechanisms underlying this comorbidity are not fully understood. Further studies are needed to better define this correlation, and broad assessment of quality of life issues, emotional states, and screening for depression in those afflicted with LUTS/BPH is encouraged.

Marijuana Usage

With the expanding legalization of marijuana and accompanying increases in usage, it is important to establish the effects of marijuana compounds on bladder, prostate function, and LUTS. Population-based studies showed that in the general population, men who use marijuana report a lower prevalence of LUTS. This effect is likely driven by the majority of younger users; however, men over 45 who use marijuana report a higher chance of requiring medical therapy for LUTS/BPH. Data from the MS population observed short-term subjective improvement in LUTS with marijuana use; it is unclear whether this effect is mediated at a CNS or organ level. There is currently limited information available to advance clinical practice and recommendations to patients when it comes to marijuana use and occurrence of LUTS, but caution certainly is prudent given that the long-term effects of prolonged marijuana use are unknown.

Erectile Dysfunction

There is a clear and distinct correlation between ED and LUTS. The pathophysiological mechanisms and causative relationships are not entirely clear, but in this instance may involve changes in the vascular tone and oxygenation of tissues in the prostate, urethra, and bladder. Established PDE5i effects in the improvement of LUTS seem to support this suggestion.

Other Patient Considerations

LUTS/BPH comprises an enormous portion of both general and urologic practice, and this disease harms a broad swathe of the general population. In order to provide the most comprehensive and holistic care for patients, an understanding of the interrelationship of LUTS/BPH and other disease states including depression, ED, and marijuana use is important. Specific advice is not able to be easily culled from the literature at present, but as

the population ages and the prevalence of marijuana use increases in adults, these topics will become ever-more important.

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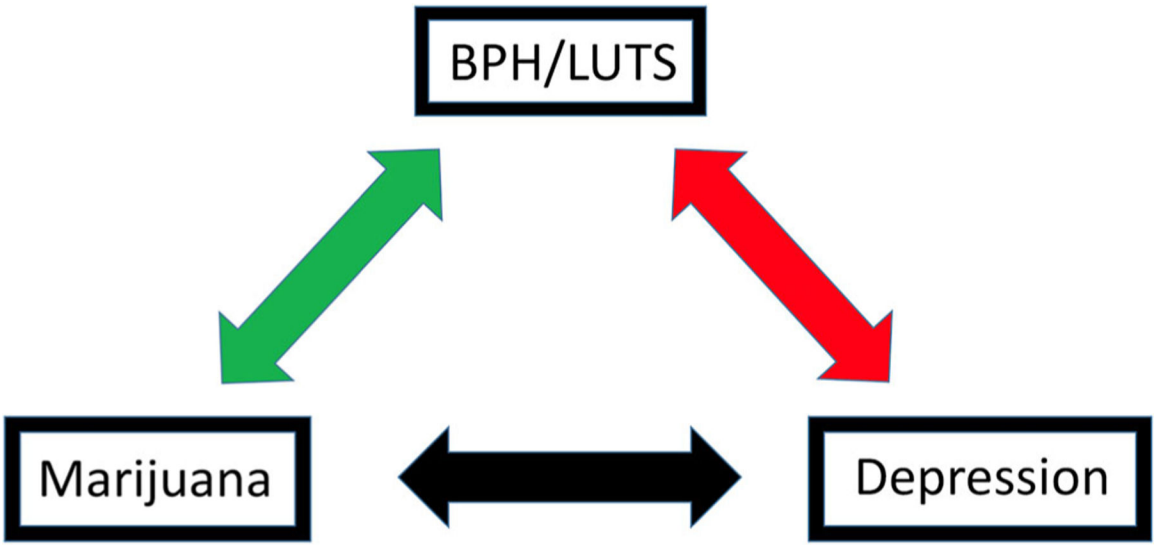

Fig. 1.

Complex interplay between LUTS, depression, and marijuana usage. A causative or primary factor has not been identified