The relationship of depression, alcohol and marijuana with treatment for LUTS/BPH

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Introduction: *Despite widespread usage, research on the relationship of marijuana use to disease is sorely lacking. We sought to test the relationship of LUTS/BPH treatment and endocannabinoid agonist usage, as well as alcohol usage and depression, with treatment for LUTS/BPH in our health system.*

Materials and methods: *We queried our hospital system database of nearly three million patients in a marijuana-legalized region for data from the electronic medical record between January 2011 and October 2018. Men over the age of 45 on medical therapy for LUTS (selective alpha blockade and/or finasteride) were included. Exclusions were diagnosis of bladder or prostate malignancy and men with only one visit. Alcohol and marijuana (MJ) use were found from diagnosis code and/or social history text. Medical diagnoses were based on ICD-9/10 codes. Multiple logistic regression was used to control for confounders. We considered all men over the age of 45 who had any of these features: depression, obesity or metabolic syndrome (MetS), hypertension (HTN), erectile dysfunction (ED), hypogonadism, diabetes (DM) and calculated the odds ratio of also receiving medical therapy for LUTS. Univariable and multivariable analyses were employed, multiple logistic regression was used to control for confounders.*

Results: *A total of 173,469 patients were identified meeting criteria with 20,548 (11.9%) on medical treatment for LUTS. After adjusting for confounding variables, MJ and depression remained associated with an increased risk of LUTS medication, within the context of verifying previously established relationships of ED, Obesity/MetS, DM, HTN and hypogonadism.*

Conclusions: *Men with depression and MJ usage were more likely to be treated for LUTS/BPH in our system. Better understanding of the causality of this relationship and potential interaction of LUTS/BPH with the endocannabinoid system is desirable.*

Key Words: BPH, voiding, LUTS, prostate, marijuana

Introduction

Benign prostatic hyperplasia (BPH) and BPH-associated lower urinary tract symptoms (LUTS) have a significant impact on men's health. Globally, LUTS/BPH causes the highest health burden of any urologic malady, malignant or benign, and threatens to rise rapidly.[1] As the population ages and the societal burden of LUTS/BPH increases, better understanding of its underlying causes and associated disease processes is vital. As a symptom complex, LUTS/BPH has multiple causative factors and many epidemiologic correlates, but an effective and unifying understanding of this heterogeneous disease has proven elusive.

As we currently lack a complete description of the pathophysiology of prostatic enlargement and of the genesis of LUTS, epidemiologic association has served researchers as an avenue to gain insight. Many relationships have been found. For example, metabolic syndrome (MetS) has been proposed as associated with the process of LUTS/BPH, although the evidence has been somewhat variable.[2] Hypertension (HTN), Type 2 diabetes (DM), obesity, physical inactivity[3] autonomic nervous system overactivity,[4] prostate growth rates and failure of senescence have all been found to contribute to, or at least correlate with, this disease. Implicating central nervous system function involvement with LUTS, depression has been linked

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with both LUTS and BPH treatment, although again the causality is unclear.[5,6]

We sought to quantify and verify the association of these disease processes in our population, and specifically in the context of the seemingly disparate factors that interact with the endocannabinoid system: depression and exogenous usage of cannabinoid agonists. Depression, as noted, has previously been observed to correlate with LUTS. Marijuana is a naturally occurring and widely used cannabinoid that has recently been legalized in a number of American states; the state of Colorado was one of the first to adopt this strategy with medical cannabis legalized in 2001 and full decriminalization in 2014, creating an opportunity for epidemiologic investigation. Aside from their highly controversial and complex effects on the human body, brain and psyche, cannabinoids have been observed to have potentially positive effects on the bladder in murine models as well as in humans with multiple sclerosis (MS).[7,8] Objective data on marijuana use and on the human effects of cannabinoids is uniquely difficult to obtain as a consequence of decades of illegality, and especially in the context of other diseases where usage and reporting can be highly confounded. Our objective was to gather data from a region with decriminalized marijuana usage for insight into the interplay of depression, LUTS/BPH, and especially marijuana and alcohol usage with the human bladder from a broad cross-section of population. We also undertook to re-verifying other previously reported correlations of LUTS/BPH as a method of validating our sample.

Materials and methods

This was a study of de-identified electronic medical record data and is considered exempt by our Multiple Institution Review Board. We queried our hospital network database (Compass Data Warehouse) of 2,855,886 unique patients for data from the electronic medical record between January 2011 and October 2018.

All men over the age of 45, including those who were on medical therapy for LUTS (selective alpha blockade and/or finasteride) were included. Dutasteride was not queried due to its very rare usage in our system. Patients with a diagnosis of bladder/prostate malignancy were excluded. Additionally, patients with only one encounter in the medical record were excluded, as these were considered to be patients who do not get routine care in our medical system and where records might be incomplete. Patients who had missing data pertaining to demographics or vital signs were also excluded, again because these were felt to be patients who did not get routine care in our medical system.

Basic demographics including current age (as of October 2018) race, and ethnicity were included. Body mass index, blood pressure, and pulse were determined from the first face-to-face encounter with these data points. Medical comorbidities including depression, obesity or MetS, HTN, erectile dysfunction (ED), hypogonadism, and DM were identified based on ICD-9/10 codes found within any encounter for that patient. Alcohol use was determined as yes/no/unspecified based on information entered in the social history from the first encounter with this data point. Marijuana use was determined based on ICD9/10 diagnosis code (any encounter) and/or social history text phrases ("marijuana", "thc", "mj", "edibles", "joint", "cbd", "weed", etc).

Medical therapy for LUTS was defined based on prescriptions in the medical record or documentation in a medications list for tamsulosin (any dose), alfuzosin (any dose) and/or finasteride 5 mg. Patients who were on medical therapy for LUTS were compared to those who were not.

Statistical analysis was completed using the R Project for Statistical Computing. Unpaired t-tests were used for comparison of continuous variables and chi-square tests with Yates' continuity correction were used for comparisons of categorical data, with a p value less than 0.05 considered significant. Following univariate analysis, variables with p value < 0.2 were carried on to multivariable analysis, and stepwise multivariable logistic regression was used to control for multiple confounders.

Results

A total of 173,469 men over the age of 45 met inclusion criteria. Median age of patients was 64 (IQR 57-72) and 78% were non-Hispanic white. Other characteristics of these men are displayed in Table 1. Of these, 20,548 (11.9%) were on some form of BPH treatment: 14,841 (72.2%) were on a super-selective alpha-adrenergic receptor blocker (alfuzosin or tamsulosin) only and 5,707 (27.8%) were prescribed finasteride 5 mg daily, alone or in combination with alpha blockade.

On univariate analysis, marijuana use was associated with increased risk of being on a LUTS medication (unadjusted OR 1.11, $p < 0.001$). Similarly, a diagnosis of erectile dysfunction was associated with increased risk of being on a LUTS medication (unadjusted OR 2.77, $p < 0.001$). Alcohol use was associated with a slightly decreased risk of being on a LUTS medication (unadjusted OR 0.88, $p < 0.001$, see Table 2.

After stepwise multivariable logistic regression modeling, Table 3, marijuana use was still associated

TABLE 1. **Characteristics of n = 173,468 men included in the study**

Race (%)	
Non-Hispanic White	135,538 (78.1%)
Hispanic	14,326 (8.3%)
Black	7,009 (4.0%)
Other	16,595 (9.6%)
Age in years (median [IQR])	64 [57, 72]
Body mass index (median [IQR])	27.9 [25.1, 31.5]
Pulse, beats per minute (median [IQR])	75 [66-86]
Systolic blood pressure, mmHg (median [IQR])	132 [120, 146]
Diagnosis (%)	
Hypertension	74,491 (42.9%)
Diabetes mellitus	35,239 (20.3%)
Depression	16,128 (9.3%)
Obesity or metabolic syndrome	18,332 (10.6%)
Hypogonadism	5,317 (3.1%)
Erectile dysfunction	8,518 (4.9%)
Any alcohol use (%)	96,657 (55.7%)
Any marijuana use (%)	10,974 (6.3%)

IQR = interquartile range

with an increased risk of being prescribed a LUTS medication (OR 1.23, $p < 0.001$) as was ED (OR 1.80, $p < 0.001$) and depression (OR 2.05, $p < 0.001$). However, alcohol use had no significant association with LUTS medical treatment and was thus dropped from the final model.

Discussion

We find men who use cannabis are more likely to be treated for LUTS/BPH than men who do not. This substance-use to symptom relationship was not present in the same group for alcohol. As there are multiple animal models that suggest the possible benefit of cannabinoids on the bladder, this association between usage of marijuana and LUTS/BPH emphasizes the question of causality: do men with LUTS tend to use cannabis to treat their symptoms? Or conversely, do men that use cannabis require treatment at a higher rate than those that do not for cannabis-induced urinary complaints? How does this relate, if at all, to baseline CNS function? Other substances of abuse can result in direct and severe urinary morbidity, for example ketamine, although this pharmacological agent is unrelated to cannabinoids and murine models of cannabinoid activity in the bladder suggest that marijuana has symptom-reducing effects and may actually ameliorate inflammation.[9]

TABLE 2. **Comparison of men (univariate) on any LUTS medication to those not on a LUTS medication**

	No LUTS medication (n = 152,920)	**Yes LUTS medication (n = 20,548)**	**p value**
Race (%)			< 0.001
Non-Hispanic White	118,632 (77.6)	16,906 (82.3)	
Hispanic	12,683 (8.3)	1,643 (8.0)	
Black	6,264 (4.1)	745 (3.6)	
Other	15,341 (10.0)	1,254 (6.1)	
Age in years (median [IQR])	63 [56, 71]	71 [63, 79]	< 0.001
Body mass index (median [IQR])	27.9 [25.1, 31.5]	27.9 [25.0, 31.4]	0.002
Pulse, beats per minute (median [IQR])	75 [66, 86]	74 [65, 84]	< 0.001
Systolic blood pressure, mmHg (median [IQR])	132 [120, 145]	132 [120, 146]	0.439
Diagnosis (%)	61,872 (40.5)	12,619 (61.4)	< 0.001
Hypertension	28,390 (18.6)	6,849 (33.3)	< 0.001
Diabetes mellitus	12,433 (8.1)	3,695 (18.0)	< 0.001
Depression	14,984 (9.8)	3,348 (16.3)	< 0.001
Obesity or metabolic syndrome	4,257 (2.8)	1,060 (5.2)	< 0.001
Hypogonadism	6,326 (4.1)	2,192 (10.7)	< 0.001
Erectile dysfunction	85,786 (56.1)	10,871 (52.9)	< 0.001
Any alcohol use (%)	9,561 (6.3)	1,413 (6.9)	0.001

TABLE 3. **Results of stepwise multivariable logistic regression modeling**

Variable	Odds ratio	95% confidence interval	p value
Non-Hispanic White (baseline)	-	-	-
Hispanic	1.11	(1.04, 1.19)	0.002
Black	0.97	(0.88, 1.07)	0.550
Other	0.67	(0.62, 0.72)	< 0.001
Age, years	1.06	(1.06, 1.06)	< 0.001
Body mass index	0.98	(0.98, 0.99)	< 0.001
Diagnosis of hypertension	1.62	(1.56, 1.68)	< 0.001
Diagnosis of diabetes mellitus	1.32	(1.26, 1.39)	< 0.001
Diagnosis of depression	2.05	(1.95, 2.16)	< 0.001
Diagnosis of obesity or metabolic syndrome	1.60	(1.51, 1.70)	< 0.001
Diagnosis of hypogonadism	1.46	(1.34, 1.60)	< 0.001
Diagnosis of erectile dysfunction	1.80	(1.67, 1.94)	< 0.001
Marijuana use	1.23	(1.14, 1.32)	< 0.001

Type 2 diabetes, obesity and MetS have previously been shown to associate with LUTS/BPH.[9] However, those associations have been variable, even to the point that some data has suggested that in Asia, MetS may be protective from LUTS/BPH.[10] Our regional data track with those seen in other studies of western men, that MetS does have a positive correlation with LUTS/BPH. Similarly, ED has been associated strongly with LUTS/BPH in multiple studies, and that also was re-verified in this dataset.[11,12] Continuing, hypogonadism has also been previously associated with LUTS, and two studies on the impact of testosterone replacement suggested improvement in voiding after replacement.[13,14]

Our primary goal was to search for a link between modulation of the endocannabinoid system and treatment for BPH/LUTS. While the systemic diseases of DM, HTN, ED, MetS and obesity have fairly clear effects on end organs such as the bladder, and may impact bladder outlet obstruction, the links to high-level CNS function are less well understood. Depression has been previously correlated with the diagnosis of LUTS in smaller patient samples. 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 defined by an IPSS score of 20 or higher.[5] Similar observations have been made in patient samples from Australia and Korea[17] and a systematic review of nocturia also found strong correlation with depression.[18] Whether this is primarily a centrally mediated effect, or whether the depressive state is a reaction to symptoms, pharmacological insult, or organ dysfunction is yet unknown.

Human research on cannabinoids in the US has been historically nonexistent, and given the absence of trials, which seems likely to continue to be the case for of this complex and socially divisive drug, we are left to try to understand its effects indirectly. Despite this paucity of evidence of the effect of cannabinoids on voiding, what data does exist suggests that it may have a salutary effect, at least in the short term. In animal models, cannabinoid agonists increase the interval between voids, pressure of voids, and flow rate.[19] Exploration of a murine model of acrolein-induced cystitis found cannabinoids to significantly counteract the chemical's irritative effects, and a role in bladder pain management has been considered.[20]

Human data also suggests that there exists an effect of cannabis on voiding and the urinary tract, and that it may in some circumstances be positive. Cannabis usage alters human bladder/ urine proteomics, including increases in immune response pathways and carbohydrate response mechanisms.[21] The meaning of these changes is unknown. A cross-sectional population study on 3,037 men aged 20-59 who completed the National Health and Nutrition Examination Survey in 2005-2008 found that self-described marijuana users reported less LUTS.[22] These findings interface in an interesting fashion with our dataset. First, the ages of men in these two groups are somewhat exclusive of each other, and it was not possible to control the NHANES data for age-related likelihood of usage. This is important because marijuana usage decreases substantially with age: 30% of adults in the 18-25 age group reported marijuana usage in the past year, but this dropped rapidly to 3.4% of those

50-64 and 0.6% of adults over 65 in data from 2002-2013.[23] It is likely that adult marijuana users represent a somewhat distinct subset in some behaviorally, socially or biologically distinct way. It may be that 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 currently possible to draw conclusions regarding effects of chronic exposure from these data.

Investigation of human cannabinoid effect in pathologic states has added perspective. Cannabinoid receptors exist in the mucosa and detrusor of the bladder, and are altered in density and distribution in the bladders of patients with idiopathic detrusor overactivity as well as in multiple sclerosis, illustrating involvement with two varied sorts of storage dysfunction.[3,8] In adult MS patients, cannabinoid pharmaceuticals appear to improve skeletal muscular spasticity and urinary function in men and women, although results have varied both by study and by formulation of cannabinoid.[26] A survey of self-selected MS patients using marijuana electively found that over half reported subjective improvement in urinary symptoms, and others have reported improvement in urge and incontinence as a benefit of cannabinoids.[8,27]

Taken together, these studies suggest that there may exist a positive impact of cannabinoids on voiding in humans, at least in the short term. The interaction becomes even more intriguing in light of the apparent relationship between depression and cannabis usage: a recent study of almost 14,000 twins from Australia has suggested a correlation between heavy marijuana usage and depression, as have others previously.[28,29] In this relationship the cause and effect is again unclear. Parallel research has suggested that an underlying deficiency in the native endocannabinoid system may be involved in heightened risk of post-traumatic stress development, and that this same endocannabinoid deficiency may result in a higher chance of self-medication with marijuana.[30] Currently, there is no indication or accepted usage for cannabinoid medications in the treatment of voiding dysfunction, whether neurogenic, in the setting of LUTS/BPH, or pure OAB. As acceptance of this socially fraught but pharmacologically simple compound grows in the medical community, we hope to see Institutional Review Boards allowing randomized controlled trials in exactly these disease states. Current usage and associated data are purely found in patient-initiated cases, and generate more questions than they answer: do patients self-medicate with cannabinoid substances to treat their own depression? To treat their own LUTS? Or do men that use marijuana find that they develop LUTS, and perhaps depression, and seek treatment from that entry point?

There are limitations of this study. As noted, accurate and scientific study of marijuana and the human endocannabinoid system has long been legally and socially nearly impossible despite clear effects on human physiology. Better understanding of these correlational findings is necessary. In this large sample, we find correlation between treatment of LUTS/BPH and the presence of multiple disease states as well as positive association of the need for treatment with marijuana use. Many of these associations have been reported previously, which is supportive of our methodology and findings. In this large clinical database of de-identified data and we are unable to verify diagnoses or medications individually and we rely on a definition of LUTS as being that which our system's physicians deem necessary for treatment – imperfect, but reflective of real-world practice. Additionally, we are also unable to quantify marijuana or alcohol usage in the men reporting it, preventing any dose-response assessment. Our definitions of cannabis usage do not capture duration of usage, although we attempted to control for reporting biases by also querying alcohol usage. Many men that use marijuana may be unwilling or less likely to report usage to their physician, even in the setting of longstanding decriminalization and established physician - patient relationship. We are unable to glean associations, provocative as they are, to chronic pelvic pain or so-called chronic prostatitis although these are such clinically heterogeneous conditions that associations would be hard to interpret.

It is impossible, at present, to know how best to put all these relationships together in the puzzle of LUTS. This triad of associated factors - marijuana usage, depression and LUTS - are interrelated and interact with each other, but a cardinal event remains to be defined, Figure 1.

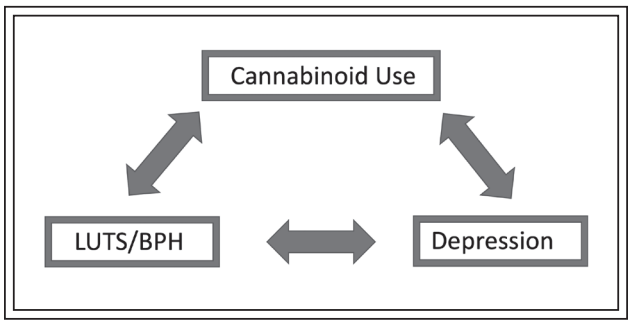

Figure 1. Complex interplay between LUTS, depression and marijuana usage. A causative or primary factor has not been identified.

Deeper assessment of the endocannabinoid system may yield answers. The moderate interaction we see between marijuana usage and LUTS treatment, if we were to consider the effect to be user-discovered therapy, might be stronger if cannabinoids were more available and considered as a prescribed, appropriate and defined therapeutic option. Whether cannabinoids are a cause of these maladies – depression and LUTS - or a common user-discovered treatment for an underlying imbalance is unknown, but a ripe area for additional exploration.

Conclusions

We verify previously reported data regarding the associations of various systemic diseases, and depression, with treatment for voiding symptoms in this large dataset, and we find a significant correlation also to exist with usage of the cannabinoid agonist marijuana, but not with alcohol. This becomes more complex with the observation that marijuana usage is also associated with depression. Whether one of these features ultimately emerges as a primary causative factor, or all are downstream events that flow from a more central cause such as deficiency of the endocannabinoid system remains to be elucidated. □

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