The Association Between Tetrahydrocannabinol and Lower Urinary Tract Symptoms Utilizing the National Health and Nutrition Examination Survey

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OBJECTIVE To further define the relationship between tetrahydrocannabinol (THC) and lower urinary tract symptoms (LUTS), specifically how THC use associates with the frequency of LUTS in young community-dwelling men in the United States.

MATERIALS AND METHODS The National Health and Nutrition Examination Survey database was queried (2005-2008). Men ages 20-59 who completed the urinary and substance abuse questionnaires were included. The presence of LUTS was defined as having ≥ 2 of the following: nocturia (≥ 2), hesitancy, incomplete emptying, or incontinence. THC use was self-reported, and participants were considered regular smokers if they endorsed smoking at least once per month. Multivariable logistic regression was performed to analyze the relationship between THC and LUTS.

RESULTS Among 3,037 men who met inclusion criteria, 14.4% (n = 477) of subjects reported THC use. In multivariable analyses, adjusting for clinical variables, regular THC users remained significantly less likely to report LUTS (odds ratio of 0.55; confidence interval 95% 0.408-0.751, $P < .01$) compared to nonusers.

CONCLUSION Obesity, diabetes, and multiple comorbidities are well-established risk factors for LUTS within the National Health and Nutrition Examination Survey. Regular THC use, however, appears to be protective from LUTS in young community-dwelling men. UROLOGY 123: 120–125, 2019.

Lower urinary tract symptoms (LUTS) plague a significant portion of the male population. While LUTS are typically associated with aging men, there remain a substantial number of affected younger men. A multinational epidemiologic study revealed that up to 51.3% of men under the age of 40 experience at least one bothersome urinary symptom.[1] There is a significant impact on quality of life as well as financial burden associated with LUTS, with an estimated $1.3 billion spent on benign prostatic hyperplasia and LUTS treatments in the United States in year 2000.[2-5]

Nearly $194 million of the aforementioned amount is spent on LUTS medications alone.[2] Pharmacotherapy with alpha-blockers has been proven effective, however, compliance has been notoriously poor with a recent study demonstrating only 29% of patients still using the drug after one year.[6] Furthermore, younger men (under 60) have been shown to have substantially lower medication compliance than their older counterparts.[7] Therefore, it is imperative to find new therapies that are not only effective in treating LUTS but also address patient compliance.

Tetrahydrocannabinol (THC) and other cannabinoids (CBs) are alternative therapies that have been shown to be effective in treating LUTS in patients with multiple sclerosis (MS) and interstitial cystitis (IC); however, their efficacy in other populations is relatively unknown.[8-12] Part of the impetus for using THC was the discovery of CB receptors in the bladder. Work in the mid 90s was able to reproducibly show decreased electrically-evoked contractions within the bladder with the use of THC.[13] A subsequent double-blinded, randomized, placebo-controlled trial verified the efficacy of THC in treating incontinence in patients with MS.[14]

Given that THC and other CBs are illicit substances in most of the US, there is no literature to date analyzing

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their effect on LUTS in young healthy men. The National Health and Nutrition Examination Survey (NHANES) was designed by the Center for Disease Control to determine the health of community dwelling individuals in the US through biannual questionnaires and physical exams. The purpose of our study was to analyze the NHANES database to determine the relationship between THC and LUTS in this unstudied population. Given the previously described mechanism of action, we hypothesized that men using THC regularly would report a decreased incidence of LUTS compared to nonregular users.

MATERIALS AND METHODS

Data Source and Study Population

The NHANES was designed as a cross-sectional data set to determine the health of the US population. Written consent was obtained from all participants and the survey approved by the National Center for Health Statistics Ethics Review Board. The 2005-2006 and 2007-2008 datasets were used because they are the only datasets that contain questions pertaining to THC use and LUTS. The study population was limited to men 20-59 years of age who answered the following questionnaires: kidney and/or urologic conditions, prostate conditions, and substance use.

Assessment of Questionnaire Data

We assessed each participant's urinary symptoms using the following questions:

1 "During the past 30 days, how many times per night did you most typically get up to urinate, from the time you went to bed at night until the time you got up in the morning?"
2 "After urinating (passing water), does your bladder feel empty?"
3 "How often do you have urinary leakage?"
4 "Do you usually have trouble starting to urinate (pass water)?"

If an individual answered ≥ 2 to question 1 they were considered to have nocturia. Similarly, if they answered "yes" to question 2 they were considered to have incomplete emptying; a response of ≥ 1 to question 3 signified urinary incontinence; "yes" to question 4 indicated urinary hesitancy. The presence of LUTS was defined as having more than one of the aforementioned symptoms.

A subject was considered to use THC regularly if they answered ≥ 1 to the question, "During the past 30 days, on how many days did you use marijuana or hashish?" Men who denied marijuana use or smoked less than one time per month were considered nonregular users.

A previously validated NHANES-specific comorbidity index was used to capture comorbid conditions. The conditions assessed included (1) arthritis, (2) congestive heart failure, (3) asthma, (4) myocardial infarction, (5), cancer, and (6) stroke.[15] Given its established relationship with LUTS within this dataset, diabetes was removed from this index and analyzed separately.[16]

Statistical Analysis

Analysis was performed using SAS 9.4 (SAS Inc., Cary, NC). We considered strata, cluster, and sample weights to account for NHANES's complex design as directed by the National Center for Health Statistics in all analyses.[17]

We combined two 2-year data sets from 2005-2006 and 2007-2008 using the unique respondent sequence number and appropriately calculated sample weighting.[17] A combination of chi-squared and t-tests were used to evaluate the demographic information on THC use and LUTS. We created a multivariable logistic regression model to look at men with ≥ 2 LUTS. Using 4-year sample weights, adjusted odds ratio (OR) and their respective 95% confidence intervals (CI) were calculated. All reported outcomes were 2-sided and considered statistically significant if $P < .05$.

RESULTS

Overall

There were 3,037 men that met inclusion criteria, of which 447 (14%) reported regular marijuana use and 1,668 (55%) reported at least one urinary symptom.

Regular THC Use

Demographics of men who reported regular THC use are compared to those who did not (Table 1). Men who used THC regularly were significantly more likely to have a normal body mass index (42.2% vs 23.8%, $P < .0001$), less likely to have diabetes (1.8% vs 5.7%, $P = .0014$), and more likely to have no comorbidities (72.5% vs 69.3%). Regular THC users were also less likely to be insured (57.7% vs 75.2%, $P < .0001$) and were less likely to have a college education (13.0% vs 27.3%, $P < .0001$).

LUTS

Demographic differences between men with and without LUTS are shown in Table 2. Men with LUTS were more likely to be obese (38.1% vs 27.1%, $P < .0001$), more likely to have diabetes (8.2% vs 1.6%, $P = .0014$), and less likely to be free of comorbidities (61.6% vs 78.6%, $P < .0001$). There was no difference in income or education level between the groups, but men with LUTS were more likely to have insurance (79.9% vs 64.6%, $P < .0001$) compared to men without urinary symptoms.

Regular THC Use and LUTS

Men who reported regular THC use were less likely to have any single urinary symptom compared to those who did not use THC regularly (40.1% vs 57.9%, $P < .0001$; Table 3a). Table 3b demonstrates that men who report regular THC use were also less likely to exhibit LUTS compared to nonregular users. The prevalence of each individual symptom was compared between regular THC users and nonregular users, however, there were no statistically significant differences (Table 3c). A multivariable model (controlling for previously demonstrated predictors of LUTS within the NHANES: body mass index, diabetes and comorbidity index) revealed that regular THC users had a decreased frequency of 2 or more LUTS (OR 0.553, 95% CI 0.408-0.751, $P < .0001$). Additionally, obesity, diabetes, and increasing comorbidity index were also shown to be significant independent predictors of LUTS (Table 4).

Table 1. Sample Demographics by THC Use

	Total (n = 3,037)		
	Regular	Nonregular	*P* Value
BMI			
Normal (20 ≤ x <25)	42.2%	23.8%	<.0001
Overweight (25 ≤ x <30)	36.0%	41.4%	
Obesity (x>30)	21.8%	34.8%	
Insurance			<.0001
Yes	57.7%	75.2%	
No	42.3%	24.8%	
Income			0.0033
<20,000	20.3%	13.3%	
≥20,000	79.7%	86.7%	
Education			<.0001
< High School	22.8%	18.0%	
High School	64.2%	54.7%	
College	13.0%	27.3%	
Diabetes			0.0014
Yes	1.8%	5.7%	
No	98.2%	94.3%	
Comorbidity Index			<.0001
0	72.5%	69.3%	
1	22.7%	23.4%	
2	3.8%	5.8%	
3	0.7%	0.9%	
4	0.2%	0.4%	
5	0.1%	0.1%	
6	0.0%	0.04%	

DISCUSSION

LUTS, while far more prevalent in men over the age of 60, still a remains a challenging problem among men aged 18-59. Causes of LUTS in this age group are often multifactorial and likely related to a combination of prostate conditions as well as systemic conditions. Historically, men in this age group have been empirically treated for conditions such as overactive bladder, nonbacterial prostatitis, and psychogenic voiding dysfunction. A recent study looked at the urodynamic findings of 308 men in this age group and discovered some degree of voiding phase dysfunction in up to 62.1% of patients.[18] While these urodynamic findings are promising, they likely do not tell the entire story. Large, granular datasets like the NHANES may be able to shed some light on the development and treatment of LUTS in this specific population.

Our hypothesis that regular THC users would be less likely to exhibit LUTS within the NHANES database was based on previous basic science studies as well as clinical trials. Pertwee et al analyzed the effect of multiple CBs (including THC) on mouse bladders. They were able to reproducibly show decreased electrically-evoked contractions of a murine bladder by agonizing prejunctional CB1 receptors.[13] Based on this study, a number of subsequent case reports, open label studies, and even randomized controlled trials were conducted on different populations.

Kren (2003) presented a case of a woman with debilitating chronic cystitis. Based on THC's analgesic effects for other pain syndromes combined with the presence of CB receptors in the bladder, she was treated with an oral CB with significant reduction in her symptoms.[10] Shortly after, Wade et al conducted a randomized, placebo-controlled, double-blinded trial using sublingual THC extract. This study looked at incontinence frequency, incontinence severity, nocturia, as well as bladder urgency. While no symptom was significant alone, when analyzed together the authors report an overall improvement in "bladder control" in the treatment arm versus placebo.[11] A subsequent single arm, open label study in the MS population validated these results. In addition, the single arm trial showed a significant decrease in the number of incontinent episodes, amount of incontinence (measured by pad weight), urinary frequency, and nocturia. A follow-up randomized, placebo-controlled trial within the MS population showed a significant reduction

Table 2. Sample Demographics by LUTS

	Total (n = 3,037)		
	LUTS	No LUTS	*P* Value
BMI			
Normal (20 ≤ x <25)	20.9%	34.1%	<.0001
Overweight (25 ≤ x <30)	41.0%	38.8%	
Obesity (x >30)	38.1%	27.1%	
Insurance			
Yes	79.9%	64.6%	<.0001
No	20.1%	35.4%	
Income			
<20,000	14.6%	14.2%	0.8158
≥20,000	85.4%	85.8%	
Education			
< High School	17.4%	19.0%	0.3262
High School	55.8%	57.2%	
College	26.7%	23.8%	
Diabetes			
Yes	8.2%	1.6%	<.0001
No	91.8%	98.4%	
Comorbidity Index			
0	61.6%	78.6%	<.0001
1	27.4%	19.6%	
2	8.5%	1.5%	
3	1.5%	0.3%	
4	0.7%	0.0%	
5	0.2%	0.0%	
6	0.03%	0.0%	

Table 3a. THC versus ≥ 1 Urinary Symptom

	Total (n = 3,037)		
	LUTS	No LUTS	*P* Value
THC Use			
Regular	40.1%	59.9%	<.0001
Non-Regular	57.9%	42.1%	

Table 3b. THC by Number of Symptoms

	Total (n = 3037)			
	LUTS = 0	LUTS = 1	LUTS ≥ 2	*P* Value
THC Use				
Regular	59.9%	31.4%	8.7%	<.0001
Nonregular	42.1%	42.6%	15.3%	

Table 3c. THC by Individual Symptoms

	Hesitancy	P Value	Nocturia	P Value	Incomplete Emptying	*P* Value	Incontinence	P Value
THC Use								
Regular	5.0%	0.7444	27.3%	0.3357	94.5%	0.1516	7.9%	0.3469
Nonregular	5.6%		31.6%		91.4%		9.4%	

in incontinence (38% cannabis extract vs 33% THC vs 18% placebo, $P < .05$).[14]

Recent murine trials have also revealed that THC can ameliorate cystitis. Wang et al described the presence of CB1 and CB2 on human urothelium. They hypothesized and subsequently proved that activation of these receptors could block inflammatory pathways in mice and resolve inflammatory cystitis secondary to acrolien.[8,9] While the exact mechanism of action in humans requires further elucidation, the idea of CB receptors as potential therapeutic targets has already affected legislation. In Illinois as of 2014, IC is now listed as a diagnosis under the "Compassionate Use of Medical Cannabis Pilot Program Act."[19]

CB receptors appear to be a promising target in the treatment of LUTS. The generalizability of the aforementioned studies, however, is quite limited. Data from the NHANES database shows a significant difference in reported LUTS between regular THC users and nonregular users (OR 0.553, 95% CI 0.408-0.751, $P < .0001$). While no one symptom was significantly different between groups, there was a trend showing that regular users had less nocturia, incontinence, and hesitancy. Interestingly, regular smokers were more likely to exhibit incomplete emptying. Based on the previous proposed mechanisms of action of THC as an anti-inflammatory as well as a bladder-relaxing agent, these findings are not surprising. Further prospective work is required to validate these findings both clinically and mechanistically.

There are numerous limitations to this study that should be noted. First, as described elsewhere, LUTS within the NHANES is limited by the number of symptom questions asked to the participants, and lacks a formal validated scale.[16,20] Second, the age group analyzed does not include men >60, which comprises a substantial number of men effected by LUTS. Additionally, given its cross-sectional nature, there is no way to identify causal relationships or chronological changes. Third, as a survey-based data set, there is always a possibility for bias. Given the illicit nature of THC, it's possible there was some degree of under-reporting, which could influence analysis. Finally, unlike approved pharmacologic options, there is no regularity to dose or type of CB inhaled in this cohort.

Table 4. Multivariable Analysis for LUTS

	OR	95% CI		P Value
THC	0.553	0.408	0.751	0.0001
BMI				
Normal (ref)	-	-	-	-
Overweight	1.578	1.283	1.940	<.0001
Obese	1.766	1.431	1.940	<.0001
Diabetes	1.925	1.242	2.985	0.0034
Comorbidity Index				
0 (ref)	-	-	-	-
1	1.600	1.250	2.048	0.0002
2	5.336	3.325	8.564	<.0001
3 or more	48.678	7.861	301.426	<.0001

CONCLUSION

There is no "one size fits all" therapy for LUTS. While medical therapies such as alpha-blockers, anticholinergics, and beta-3 agonists have all made significant improvements in patients' quality of life, compliance is often poor and many people continue to suffer. THC has been previously used in patients with MS and IC with good results, but there is currently no data about its use in healthy young men. This large cross-sectional dataset is able to provide insight into a possible new alternative therapy in young men with LUTS. Further prospective randomized controlled trials are needed to validate these findings, determine the side effect profile, and determine the feasibility of THC as a possible treatment for LUTS.

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EDITORIAL COMMENT

The authors explore the National Health and Nutrition Examination Survey database regarding the use of tetrahydrocannabinol (THC) and lower urinary tract symptoms (LUTS). This is a very interesting and contemporary subject due to the ongoing discussion on marijuana legalization.

From statistical analysis, they could conclude that THC usage decreases the LUTS. Criticism on the paper should be put on the fact that THC usage was self-reported and even an infrequent usage such as once a month was included as significant in comparison to nonusers.

As there is biochemical evidence of cannabinoid receptors in the detrusor with exquisite inhibitory properties, urologists need to be cognizant THC might be incorporated to the armamentarium to deal with LUTS or for special situations as the ones already in use as for to treat some terminal urological cancer cases or incontinence in multiple sclerosis cases.

SUGGESTED READING

Freeman RM, Adekanmi O, Waterfield MR, Waterfield AE, Wright D, Zajicek J. The effect of cannabis on urge incontinence in patients with multiple sclerosis: a multicentre, randomised placebo-controlled trial (CAMS-LUTS). Int Urogynecol J Pelvic Floor Dysfunct 17(6):636-41, 2006

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AUTHOR REPLY

Based upon epidemiological data from the NIH, it has been reported that marijuana is the most widely used illicit drug, with over 22.2 million people using it within the past month.[1] Given increasing pressures to legalize this drug in multiple states, there is an urgent need to elucidate its potential medical benefits versus unrecognized side effects.

One of the main limitations of research on this subject is specifically defining which chemical compounds in marijuana are active and how to generalize the data based upon the frequency and type of use. Unless a clinician is prescribing a specific cannabinoid, most strains of marijuana have a heterogeneous profile containing multiple different cannabinoids as active compounds.[2] Therefore, defining regular usage in the present cohort is difficult not only based on a subject's frequency of use but also because each chemical concentration level may vary.

While there is no standardized definition for "regular use," recently proposed definitions vary from weekly to four or more times a week.[3-5] While our manuscript includes people that may only smoke once monthly, research also suggests that the chronicity of use may also affect patients.[5] A well-designed prospect trial however, similar to prior studies looking at specific types of patients, using a regulated dose at a regular frequency, could better answer this question.[6,7] It would be beneficial to discover the minimum tetrahydrocannabinol and/or appropriate cannabinoid dose, as well as dosing schedule, to provide patients with lower urinary tract symptom relief while minimizing potential undesirable side effects.

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