

General

Lower Urinary Tract Symptoms in Depression: A Review

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Lower Urinary Tract Symptoms (LUTS) are frequently present in the general population as patients age with approximately a third of individuals experiencing LUTS during their lifetime. LUTS can be further defined as having any of the following symptoms: urinary hesitancy, straining, nocturia, increased urination frequency, and dysuria. LUTS has the potential for patients to contribute their symptoms to what can normally occur as we age. This can lead to a decrease in patients seeking care and could negatively impact patients' health-related quality of life (HRQL). In conjunction with LUTS, we obtained from our analysis that LUTS and depression are closely related and worsening depressive symptoms may increase the severity of LUTS. We also discerned three categories of factors that can yield major depression namely adversity, internalizing, and externalizing factors. Within these categories, trauma, social support, genetic factors, and minimal education appeared to increase the risk of depression in patients. With the recent increase in mental health awareness and more access to mental health care amid the COVID-19 Pandemic, further screening, and collaboration between providers to treat both urological and psychiatric symptoms could improve patient outcomes. It is important for providers to have an increased understanding of the mental and physical impact both LUTS and depression can have on patients' wellbeing. This has the potential to help patients be more open about their symptoms with the aim of better addressing LUTS and depression to positively impact their HRQL.

INTRODUCTION

Lower urinary tract symptoms (LUTS) are a common complaint among men. It was reported that 3 in 4 men ages 60 to 69 had nocturia while at least 80% of men had a LUTS complaint by age 80.¹ LUTS are classically divided into three categories including storage, voiding, and post micturition (sensation of incomplete emptying of the bladder).² Storage symptoms include urgency, daytime frequency, nocturia, incontinence, and abnormal bladder sensation, while voiding symptoms include slow stream, intermittent stream, hesitancy, straining to void, and dysuria.² LUTS have several methods of treatment, but the success rates are variable and are associated with high costs

to the health care system and the individual.³ LUTS have been shown to negatively impact a person's HRQL along with increasing their risk for functional decline, falls, and other diseases.⁴ LUTS are most classically associated with prostate abnormalities and bladder deterioration, but recently a few studies have shown that LUTS are associated with many systemic diseases like obesity, type 2 diabetes, and even depression.^{2,5,6} Depression is a common condition that has a prevalence of 16.5% and has been shown to be associated with many chronic diseases such as urologic diagnoses specifically incontinence.⁷ Studies have also shown that depression has been associated with LUTS in a unidirectional and bidirectional relationship.^{2,4,8,9} In a population-based study in Korea, it showed that depressive

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symptoms were more common in men (11.5%) with LUTS compared to men without LUTS (2.9%).⁴ Patients with LUTS and depression have shown to have increased severity of symptoms and a decrease in overall quality of life.¹⁰⁻¹² This article will be a review on the bidirectional relationship between LUTS and depression that has been demonstrated from multiple studies and types to include: systemic reviews, meta-analyses, and longitudinal studies.

DEPRESSION

EPIDEMIOLOGY

Mental disorders are highly prevalent all over the world and can be critically disabling. In the United States, epidemiological surveys have shown that anywhere between 26% and 30% of adults meet criteria for a mental health disorder.^{13,14} A study on prevalence and severity of mental health disorders demonstrated that major depression made up 6.7% of all respondents.¹⁴ Of the 6.7%, 30.5% were serious, 50.4% were moderate and 19.5% were mild cases of major depression.¹⁴ In the study of prevalence and severity it was also revealed that the more severe the case the higher the comorbidity was in that group.¹⁴ Studies have further gone to reveal that in the population, major depression gets more prevalent as age increases; specifically for individuals over the age of 75.^{15,16} One study showed that for the cohort of ages 60–66 depression was 4.4% of the studied group and increased to 25.7% at the ages of approximately 90 to 104.¹⁵ Major depression is an episodic disease that can re-occur in up to 50% of the patients who seek treatment, and a recent study has shown that every recurrence of major depression increases the chance by 16% of it making an appearance in the future of that individual.¹⁷ The high prevalence of mental disorders in the United States leads to significant burden on the health care system and the person. A study on the burden of diseases has shown that as a nation we have increased the average life span; however, the years of living with a type of disability has increased from 9.4 years to 10.1 years.^{18,19} In a global study on disease burden, it was demonstrated that the shift from communicable diseases that cause premature death has shifted to non-communicable diseases like mental disorders and metabolic disorders leading to an increase of years living with disability.¹⁹

PATHOPHYSIOLOGY/RISK FACTORS

Depression is a mood disorder that is classified as a multifactorial disorder due to its range of risk factors that lead up to the increased severity of disease.²⁰ The pathogenesis of major depression appears to involve three sets of risks factors according to the developmental model study, which include internalizing factors, externalizing factors, and adversity factors.²⁰ The internalizing risk factors encompass genetic factors, neuroticism, low self of esteem, early onset anxiety, and history of major depression.²⁰ Externalizing factors include genetic factors, conduct disorder, and substance misuse.²⁰ Adversity factors comprise low parental warmth, childhood sexual abuse, parental loss, low educa-

tion lifetime trauma, low social support, marital problems, and stressful events.²⁰ A person with elevated genetic risk factors is more likely to be exposed to risk factors at higher rates and more likely to put themselves in stressful situations in adulthood.²⁰ A national comorbidity survey study has shown that child adversities have increased risk of developing a disorder like depression in childhood compared to adulthood at 44.6% rather than 28.6% in adults.²¹ A Sweden study revealed that a preterm birth between 32 to 36 weeks compared to 37 to 41 weeks was 34% more likely to have a depressive disorder and those less than 32 weeks were three times as likely.²² It was also discovered through research that an Apgar score lower than 3 has the severe effect of doubling the risk for depression.²² Lastly, a couple studies have elaborated on a weak association of low birth weight and increased risk of depression but have not been proven statistically significant due to alcohol, drugs and other cofactors.^{22,23}

LOWER URINARY TRACT SYMPTOMS

EPIDEMIOLOGY

Lower urinary tract symptoms (LUTS) is a nonspecific term that encompasses two categories: voiding disturbances, including straining, weak stream, and urinary hesitancy and storage disturbances, including nocturia and urinary urgency. The Epidemiology Urinary Incontinence and Comorbidities (EPIC) study, the one of the largest population-based survey assessing prevalence rates of LUTS, found that more than 60% of the general population experiences at least one LUTS with the most prevalent symptom being nocturia.²⁴ The high prevalence and associated health burden rendered by LUTS makes studying the specific populations affected important to identify disease courses and a baseline for diagnosis.

The severity and prevalence of LUTS increases with age for both men and women.^{25,26} This relationship between age and LUTS is maintained over the age of 80 years and is associated with increased urgency, weak urination, increased frequency, and incomplete voiding compared to younger populations.²⁷

Furthermore, relationships between other comorbidities and LUTS exist. Studies have identified a significantly greater prevalence of LUTS in diabetics compared to the general population with the duration of disease being an important risk factor.²⁸ A correlation among LUTS, cardiovascular disease, and metabolic syndrome has also been established.^{29,30}

Various modifiable risk factors contribute to an increased risk of LUTS. Obesity, cigarette smoking, and alcohol intake are strongly associated with LUTS.^{25,30,31} Furthermore, Luke *et al.* observed that bariatric surgical patients that were pre-operatively complaining of LUTS had improved symptoms post-operatively, suggesting a possible reversal effect of the obesity and LUTS association.^{25,31}

Genetics may explain the prevalence of LUTS in certain populations. For instance, specific single nucleotide polymorphisms in β -3 adrenoreceptors and collagen have been

identified as risk factors for overactive bladder syndrome and urinary incontinence, respectively.²⁵ This heritability may help explain the recurrent incidence of LUTS in some individuals.

PATHOPHYSIOLOGY/RISK FACTORS

Various etiologies are associated with the development and progression of LUTS and typically display a characteristic course. Bladder outlet obstruction (BOO) is a major cause of the voiding-type LUTS. In men, bladder outlet obstruction is most commonly caused by benign prostatic hyperplasia.^{32,33} BPH affects approximately 50% of men over 40; about half of these men develop LUTS.⁵⁴ In women, bladder obstruction is commonly caused by previous incontinence surgery or pelvic organ prolapse.^{35,36} Other less common causes of BOO include neurogenic dyssynergia and congenital anomalies.³⁶ Regardless of the cause, BOO increases the resistance of urine outflow, leading to a high postvoid residual (PVR) urine and urinary stasis.³⁵⁻³⁷

Etiologies mainly affecting bladder storage are also common. OAB is a storage symptom syndrome characterized by urinary urgency with or without urge incontinence, urinary frequency, and nocturia.^{38,39} Normally, signals from the brain alert adults when the bladder is about halfway full.¹⁵ Individuals with a healthy bladder function can postpone urination until an appropriate time. Conversely, patients with OAB feel a sudden urge to urinate even if the bladder is not full.³⁸ This urgency may be caused by premature signals from the brain to empty the bladder or recurrent, uncontrolled bladder contractions.³⁸ Detrusor overactivity refers to a urodynamic observation characterized by uncontrolled detrusor contractions during the filling phase.^{39,40} Detrusor overactivity can be categorized based on the identified etiology, namely idiopathic or neurogenic, and the type of contraction, namely terminal or phasic.³⁹ Although phasic contractions may or may not result in urinary incontinence, terminal contractions often lead to complete emptying of the bladder.³⁹

ASSOCIATION BETWEEN DEPRESSION AND LOWER URINARY TRACT SYMPTOMS

LUTS are a significant but hidden burden on aging male populations. 50% of men over 50 will experience some form of LUTS including sometimes overlooked conditions such as BPH.⁴⁰ It is further estimated by the UN and speculated on by Nishii H. that 80% of the aging population will be in underdeveloped areas.^{40,41} This is troubling for several reasons: 1) Mental health is widely underserved around the world, even in developed countries.⁴²⁻⁴⁴ 2) Around 33% of people by age 50 will develop some form of LUTS with it becoming essentially a matter of fact for men as they continue to age.^{40,45-68} 3) There is a known association between depression and LUTS.^{40,47,48,50-52,54-62,66-125} The question we seek to answer is can depression actually cause LUTS?

LUTS are present in at least 40% of men for extended periods of time which lead to significant impacts on HRQL.^{40, 45,46,48,56,58,59,62,66-68,70,72,76,78,82,85-87,90,92,93,96-98,104,}

108,109,111-115,118,120,122,124,126,127 HRQL is closely linked with mental wellbeing, including somatic symptoms and issues such as anxiety and depression. This is further amplified when the condition that needs to be addressed is obvious to the patient but not those around them.^{51,54,56,70, 72,77-79,84-88,93,94,97-100,102,103,108,126,128-130} This point is emphasized by the wealth of research on related (disabilities not outwardly visible) forms of disability such as neuropathic pain, MS, depression, myasthenia gravis etc.⁹¹⁻⁹⁷ There is a clear association between LUTS, and depression as addressed earlier, but is depression causing the LUTS, is it the other way around, or is there a confounding factor that we remain unaware of? In a review of the recent literature on the topic it is known that there is a bidirectional component.^{40,51,53,54,58-62,66,67,69,70,76,78-80,84,86,90,92-98, 101,102,104,106-116,118-122,126-129,131-136} A clear temporal relationship is beginning to be investigated that shows some evidence of depression predating urologic symptoms.^{56,61,67,78,80,94,97,98,102,104,108,111-114,116,118,127,129} I would like to highlight several studies that have data to suggest that depression can independently cause LUTS.^{51, 62,66,79,90,97,106,108,115,116,121,122,127,132,134} Of these studies, I would like to specifically highlight the association between BPH and suicide in South Korea and the mouse model of psychological stress inducing bladder overactivity in female mice.^{115,132} The BPH and suicide study was a retrospective look at men who had committed suicide over a 9-year period evaluating 193,785 Korean adults. Lee et al. found a significant hazard ratio that indicated that BPH alone was 1.5 times more likely to lead to suicide. This heightened risk was present even when addressing confounding factors such as age and socioeconomic status until the age of 70.¹¹⁵ This association was also present when Lee et al. stratified the data to look at BPH in individuals without other mental conditions. This data suggests that the initial biological insult in the patient population may be the LUTS. From this perspective, Lee et al. argue that the diagnosis of LUTS leads to decreasing HRQL in aging men which takes away their agency and ability to perform their societal roles leading to depression.¹¹⁵ We have already established the bidirectional association between depression and LUTS. Therefore, it is necessary to evaluate the intriguing evidence presented by Millis et al. in their paper on stress inducing bladder overactivity in female mice. They found after a 10-day period of inducing water avoidance stressors that the female mice approximately doubled their voids with no significant difference in amounts voided.¹³² They found a measurable difference in the afferent nervous system response between the stressed mice and control group.¹³² This evidence is relevant despite being in a mouse model as it shows a direct causation pathway. Stress induced LUTS in this mouse model.

It is sometimes difficult to apply models to human physiology. To draw conclusions let us examine a different set of data. There is evidence that children with LUTS have decreased HRQL compared to their peer groups.^{133,137,138} Trauma is also a risk factor for long term LUTS.^{101,136,139} This information examined in the context of the mouse data is sufficient to suggest a deeper connection. Long-

standing or childhood trauma already sets people up to have an increased rate of LUTS down the road compared to the general population. These experiences are also a risk factor for anxiety and depression. This added to the mouse model suggests that stressful life events are indeed enough to induce LUTS and helps further define the association between mental health and LUTS. Previous evidence was sufficient to suggest that a multimodal approach was necessary to fully treat patients with LUTS.^{79,82,97,112,113,115,119,133,139} Thinking beyond what was demonstrated in the mouse study, other studies have noted a bidirectional relationship among LUTS, depression, and anxiety to list a few factors. This is further expounded upon with the idea that there might be more biological and psychosocial connections in relation to LUTS and understanding these potential pathways could be an area for future research.¹⁴⁰⁻¹⁴³ Taking this information together, it is necessary then to treat both the mind and body to help these patients. Stress can and will lead to somatic symptoms as proven by the mouse model.¹³² It is necessary to address patients, especially aging men from a perspective that they may not be fully disclosing the extent of their symptoms. The link between BPH and suicide further suggests that someone's life may very well be at risk due to not sufficiently treating their underlying condition.¹¹⁵ Evidence from chronic diseases shows that they must be addressed holistically or risk poor patient care.¹⁴⁴⁻¹⁴⁶ It is necessary to remind and educate patient populations that their symptoms may very well be more serious than they would initially believe and are likely contributing negatively towards their overall health.

CONCLUSION

Numerous studies including systemic reviews, meta-analyses, and longitudinal studies have demonstrated a bidirectional relationship between depression and LUTS.¹⁴⁷⁻¹⁴⁹ Evidence showed that patients with LUTS had a significantly higher risk of depression compared to those without LUTS.¹⁹ Similarly, patients with depression displayed a higher risk of developing LUTS with the risk proportionally increasing with worsening depressive symptoms.¹⁴⁹⁻¹⁵¹ A positive correlation between the severity of depressive symptoms and the exacerbation of LUTS based on both the perception of symptoms and measured urodynamics has been identified.^{140,141} The strong association between depression and urinary symptoms suggests a related biological pathway between psychosocial factors and bladder function. Postulated biological mediators in this association consist of the hypothalamic-pituitary axis, the sympathetic nervous system, and inflammation.^{140,142,143}

The high prevalence of depression in patients with LUTS emphasizes the importance for health care providers to screen for depression in those with chronic urinary symptoms. The presence of both conditions may require clinicians to adopt an interdisciplinary approach involving urology and psychiatry for the management of LUTS. Treating the depressive symptoms may have considerable positive therapeutic effects that would be neglected by simply targeting the bladder.¹⁴⁹ Additional studies investigating the intersecting biological pathways of depression and LUTS can help clinicians discover the most promising treatment regimens.

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