# Relationship Between Depression and Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia

**Claire Dunphy, BA, Leanna Laor, MD, Alexis Te, MD, Steven Kaplan, MD, Bilal Chughtai, MD**
Department of Urology, Weill Cornell Medical College, New York, NY

This article provides an overview of current data on the relationship between depression and lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH), with a focus on pathophysiology and patient management implications. Review of the literature indicated a clear relationship between LUTS secondary to BPH and depression. It is unknown whether this relationship is bidirectional or unidirectional. Depression is associated with the impact of LUTS on quality of life in men with BPH. Research suggests that depression alters the experience of LUTS in this population. Medical and surgical treatments for BPH may impact quality of life and, therefore, depression. Results conflict on the exact nature of the relationship examined, and on the extent to which the relationship may be attributed to physiological factors such as inflammation. Practicing clinicians should consider using a brief self-administered scale to assess for depression in patients with BPH. There is a clear need for additional research to decisively determine the nature of the relationship between LUTS secondary to BPH and depression, as well as the extent to which change in either condition may be affected by the other.

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**KEY WORDS**

Benign prostatic hyperplasia • Depression • Lower urinary tract symptoms

The prevalence of benign prostatic hyperplasia (BPH) increases with age.[1] Approximately half of men over age 40 are diagnosed with BPH. Of these men, approximately 50% will develop significant and bothersome lower urinary tract symptoms (LUTS) secondary to BPH, which increase in prevalence between ages 40 and 80 years. LUTS secondary to BPH is associated with decreased quality of life and may include urgency/frequency, incontinence, and nocturia. Symptom severity is impacted by the degree of prostatic enlargement, which is highly variable.[1]

Depression is another common condition that severely and negatively impacts quality of life, with an estimated lifetime prevalence of 16.5% according to the National Institute of Mental Health.[2] Depression plays a role in the pathogenesis of a number of chronic diseases, including inflammatory bowel disease, arthritis, asthma, and diabetes[3]; a relationship has also been identified between depression and urologic diagnoses such as incontinence.[4] Symptoms of BPH are associated with decreased quality of life and depression, and the literature strongly suggests that there may also be a pathophysiologic relationship between BPH and depression[5,6]; in addition, depressive symptoms are also associated with treatments for BPH.[7-9]

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Research has suggested that psychiatric parameters such as depression may have a putative role in the development of LUTS secondary to BPH.[6] Furthermore, depression may pose an impediment to effective treatment for these patients. Improved understanding of the relationship between BPH and depression could lead to improved management. This area of research is important because clinical depression is associated with a significant increase in mortality, and early detection, intervention, and treatment of clinically relevant depressive symptoms are key factors in patient care.[10]

Fewer studies have focused on the relationship between depressive symptoms or depressive disorders and BPH, or the nature and direction of this relationship. Thus, a systematic review of the relationship between depression and BPH is needed. We provide a comprehensive summary of contemporary published reports on LUTS secondary to BPH and depression to improve understanding of the relationship between these two conditions and provide a framework for future investigation.

## Search Methods and Evidence Acquisition

A systematic literature search in PubMed was performed. The following terms were used: *benign prostatic hyperplasia*, *benign prostatic enlargement*, *depression*, and *lower urinary tract symptoms*. Abbreviations (*BPH*, *BPE*, and *LUTS*) were also used. Searches were limited to articles on adults published in English. Relevant citations from articles selected under these terms were also included. Each article's title and abstract were reviewed for their appropriateness and relevance to the relationship between depression and BPH. Relevant articles were fully reviewed to assess study design and the amount of evidence, and were included in the final data acquisition.

## Pathophysiology of BPH/LUTS and Depression

Several physiologic mechanisms have been proposed that may account for a relationship between depression and LUTS secondary to BPH. One possibility is that central physiologic abnormalities such as increased adrenergic tone, which cause depressive symptoms, may also contribute to urologic symptoms.[11] Johnson and colleagues inferred that chronic inflammation may be a possible common cause of these two diseases.[5] It is well known that inflammation contributes to the pathophysiology of major depression[12]; depressed patients often exhibit significant increases in inflammatory biomarkers such as C-reactive protein, interleukin-6, and tumor necrosis factor-α. These inflammatory pathways might also contribute to the relationship between depression and other inflammatory disease states. Additional data have even suggested a bidirectional relationship between depression and inflammatory disease states, and it is possible that this association could extend to LUTS secondary to BPH.[13,14] There is speculation that depression and LUTS secondary to BPH are linked with certain neurotransmitters that also play a role in depression, possibly contributing to the development of clinical

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symptoms and even treatment outcomes in patients with LUTS secondary to BPH.[6]

## Relationship of BPH and Depression

### *Association of LUTS and Depression*

Previous research has established that LUTS increase the odds of having depressive symptoms. Wong and colleagues[15] found that, in elderly men, moderate to severe LUTS are associated with an increased risk of having clinically relevant symptoms of depression. In the Epidemiology of LUTS (EpiLUTS) study—a cross-sectional, population-based examination of LUTS—depression was found to be a frequently comorbid condition for men with LUTS.[16] Laumann and associates[11] found, in a nationally representative sample of nonhispanic white, nonhispanic black, and Hispanic men, that depressive symptoms were significantly associated with increased odds of LUTS. In a cross-sectional, population-based study, men with LUTS had an increased risk of reporting not only depression, but suicidal ideation as well. In addition, men with more severe depression measured by the Patient Health Questionnaire-9 (PHQ-9) were at greater risk of having LUTS.[17]

It is possible that other factors, such as ethnic background, could play a role in this relationship. In an analysis by Laumann and colleagues,[11] the interaction between LUTS and depressive symptoms was most robust in Hispanic men (odds ratio [OR] 4.69; 95% confidence interval [CI], 1.49-14.75; $P < .01$). The authors suggested that this finding might be attributed to genetic factors associated with major depressive disorder and its remission in response to antidepressants. Alternatively, it is feasible that Hispanic men with depressive symptoms might be relatively more willing to report LUTS than those without depressive symptoms.[11] A possibility is that minorities with either disorder may be at greater risk for depressive symptoms and/or LUTS, but additional research is needed.

The finding that LUTS increases the probability of depressive symptoms is intuitive, because LUTS are associated with decreased quality of life and interference with daily activities. The relationship between depression and nocturia, a specific subset of LUTS, has been reviewed previously.[18] Although most of the previous research has focused on the impact of LUTS on quality of life, fewer studies have focused on the relationship between depressive symptoms or depressive disorders and LUTS secondary to BPH, or the nature and direction of this relationship. Overall, we found that BPH increased the probability of reporting depression, and depression similarly increased the likelihood of reporting LUTS secondary to BPH. The majority of studies reviewed were classified as Level of Evidence IV.

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### *Impact of BPH on Depression*

Several studies provided evidence on the impact of LUTS secondary to BPH on depression. Huang and coworkers[10] prospectively collected Taiwanese population-based data to help determine the relationship between BPH and depressive disorder. A cohort of 64,520 men was studied during a 1-year period, including 16,130 participants with newly diagnosed BPH. The control group consisted of 48,390 matched enrollees who had no history of BPH. Of the total number of patients, 856 (1.33%) were diagnosed with depressive disorder during the 1-year follow-up period; this included 325 (2.01%) from the patient group with BPH and 531 (1.10%) from the control group, suggesting that the likelihood of being diagnosed with depressive disorder was 1.87 times greater for patients with BPH during the year following diagnosis (95% CI, 1.63-2.16; $P < .001$). These findings suggest a unidirectional effect of BPH on the incidence of depressive symptoms and subsequent diagnosis of depressive disorder. Another prospective study included 1726 Chinese men aged ≥ 65 years to elucidate the temporal relationship between LUTS and clinically significant depressive symptoms. Using International Prostate Symptom Score (IPSS) to assess LUTS and the Geriatric Depression Scale to assess depression, the authors found that the presence of moderate to severe LUTS at baseline was associated with an increased risk of clinically relevant depressive symptoms at 2-year follow-up (OR 3.25; 95% CI, 1.91-5.52).[19]

### *Impact of Depression on BPH*

Other studies have provided evidence on the impact of psychiatric parameters, specifically depression, on the clinical manifestation of LUTS secondary to BPH. A Korean population-based study including 392 men aged ≥ 65 years found that elderly men with depression are likely to have more severe LUTS than those without depression, particularly if urinary

urgency is present.[20] It is possible that this relationship may extend to treatment response as well. Yang and associates[6] conducted the first study to investigate the influence of depression, anxiety, and somatization on clinical symptoms and treatment response in 93 patients with diagnosis of LUTS secondary to BPH. Validated rating scales including the PHQ-9 and the seven-item Generalized Anxiety Disorder Scale were used to measure psychiatric parameters of depression, anxiety, and somatization. Symptom severity of LUTS secondary to BPH was assessed using the IPSS. Patients with depression had a significantly higher total score than those without depression (18.5 vs 15.3; $P = .046$), indicating greater symptom severity. In a study examining risk factors for the progression or improvement of LUTS suggestive of BPH in 780 men between ages 35 and 80 years, depression was associated with an increased risk of LUTS progression independent of other lifestyle and medical factors. Depression at baseline, which was defined by self-report, Beck Depression Inventory score, and/or use of antidepressants, preceded progression of storage and voiding symptoms over 5 years.[21]

Another factor to consider in the relationship between depression and BPH is the possibility that depressed patients may report elevated subjective symptom scores due to the tendency of these patients to catastrophize. A cross-sectional study with 547 men enrolled with a reported mean age of 59.2 ± 15.1 years was conducted.[5] Patients were placed into two groups based on their answers to the Geriatric Depression Scale (GDS); nondepressed patients had a GDS score ≤ 5 and depressed patients had GDS scores > 5. Of the entire cohort, 22% of patients screened had depression (GDS > 5). Compared with the nondepressed patients, depressed patients reported significantly higher American Urological Association Symptom Index (AUA-SI) scores (16.61 ± 9.89; $F = 40.19$; $P < .001$), which assesses the symptoms commonly present with BPH. Of the nondepressed patients, most fell into the categories of mild or moderate AUA-SI scores, whereas more than two-thirds of the depressed patients presented with moderate (37.5%) and severe (41.3%) AUA-SI symptoms. On univariate logistic regression, age, income, homelessness, and depression were significant predictors of presenting with severe symptoms, whereas on multivariate analysis only depression remained statistically significant. After adjusting for age, income, language, employment, and homelessness, depressed patients were three times more likely to present with severe symptoms (OR 3.079; 95% CI, 1.129-8.402; $P = .028$)

### *Reciprocal Relationship Between BPH and Depression*

The direction of causation remains unclear. Aside from the theories of potential pathophysiologic relationship between depression and LUTS in men with BPH, one hypothesis is that the negative impact of LUTS on quality of life in men with BPH results in the development of depression. It is well known that chronic illnesses can lead to depression, and it has been established that LUTS secondary to BPH can seriously impact quality of life. LUTS may also lead to depression indirectly through sleep deprivation caused by nocturia, a major LUTS subset. It is also possible that depression plays a role in the subjective severity of BPH symptoms, particularly in the context of depressed patients' tendency to catastrophize. Depressed patients might report subjective suffering or greater AUA-SI scores than represents their true pathologic state. Considering the evidence that exists to support an impact of LUTS on depression, as well as the impact of depression on LUTS, a final hypothesis involves a reciprocal or bidirectional relationship. Several studies have demonstrated that depression in the setting of cardiovascular disease and cancer actually worsens these chronic disease states.[3,14] Perhaps LUTS triggers depression in men with BPH, which in turn exacerbates LUTS severity and results in worsening depression.

## BPH Treatment and Depression

Treatments used for patients with LUTS secondary to BPH may be associated with depression as well. Frequently used medications to treat LUTS secondary to BPH include 5-α-reductase inhibitors (5-ARIs; eg, finasteride and dutasteride) and α-adrenergic antagonists (α-blockers; eg, prazosin, terazosin, doxazosin, and alfuzosin).[1] The gold-standard surgical treatment for BPH is transurethral resection of the prostate (TURP).[6] Side effects of these treatments, which may include incontinence and erectile dysfunction (ED), may contribute to depression. ED, a potential side effect of treatment with either medical therapy or TURP, has been found to

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be associated with increased rates of LUTS and depression.[11]

### *5-ARIs and Depression*

5-ARIs have been approved for the treatment of BPH and the subsequent LUTS that develop.[7] Adverse effects on sexual function, depression, and quality of life are associated with the use of these medications. Studies have reported that 5-ARIs contribute to reduction or loss of libido and ED.[7] Psychological impact may be explained by an association between depression and androgen deficiency, which may occur as a result of the medication. Low androgen levels are associated with symptoms of irritability, dysphoria, increased risk of depressive symptoms, and depression.[7]

### *α-Inhibitors and Depression*

In response to several reports of depression associated with α-inhibitor medications used for the treatment of LUTS secondary to BPH, Clifford and Farmer[9] conducted a cohort analysis in which the risk of depression in patients with BPH was assessed, as well as the risk of depression in those exposed to α-inhibitor medication.[9] It was found that the risk of depression was significantly higher in men with BPH compared with those without BPH (incidence rate ratio 2.17, 2.12-2.22). However, there was no significant difference for those men exposed to α-blockers in comparison with those who were not exposed. Patients with depression were more likely to have preexisting BPH than the control group (crude OR 2.09, 2.02-2.15). When adjusting for preexisting medical conditions and the presence of BPH, there was no significant connection between the use of α-blockers and depression (adjusted OR 1.03, 0.90-1.18). The study concluded that the relationship between depression and exposure to α-blockers is confounded by concurrent disease states.

### *TURP and Depression*

In a study by Quek and colleagues,[8] 123 men (mean age 64.6 years) were treated using α-blockers for BPH; 52 men (mean age 69.6 years) were treated using TURP. Both patient groups were assessed for anxiety, depression, and psychiatric morbidity before treatment and 3 months after treatment. The Beck Depression Inventory, the State Trait Anxiety Inventory, and the General Health Questionnaire-12 were used. Results of the study showed that, prior to treatment, patients who went on to receive TURP were more depressed than patients who received medication. After treatment, both groups showed improvement in depression levels, although this finding was not statistically significant. Patients in the TURP group demonstrated a significantly better improvement in depression levels after treatment. This could possibly be attributed to the failure of medical treatment to alleviate urinary symptoms to the extent of surgical treatment. TURP patients also had significantly higher psychosocial morbidity scores prior to treatment. Psychiatric morbidity significantly improved in the TURP group but not the medication group ($P < .001$). Severe depression level for patients who underwent TURP slightly increased immediately after surgery, possibly due to surgical complications, which may include incontinence, retrograde ejaculation, and impotence.

## Patient Treatment Implications

Understanding that BPH and depression are frequently comorbid has important implications for the treating clinician. Rom and colleagues[22] recommended that clinicians screen for depression in all patients presenting with LUTS suggestive of BPH, as well as for LUTS in patients presenting with depressive symptoms. In addition, patients who screen positive for mental health disorders including depression may benefit from referral to an appropriate provider, such as a psychiatrist, psychologist, or social worker. Patients who screen positive for depressive disorder may require more extensive counseling before diagnostic testing or surgery. Clinician insight into the patient's emotional state may promote improved communication and prevent patient dissatisfaction with treatment. The response to medical management for BPH may be improved by also treating the underlying mood disorder.

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In a study by Beyramijam and associates,[23] patients with BPH who were candidates for TURP were included in a study of the impact of a self-care educational program on anxiety, stress, and depression in this population. The authors found that, in the group of patients who received the self-care educational program, there was a decrease in depression in comparison with the control group. Although nonsignificant ($P = .082$), these results may suggest that

interventions may be helpful for patients about to undergo TURP, particularly for those who screen positive for depression.

## Future Directions and Conclusions

A high level of depressive symptoms and other psychiatric morbidity have important implications for management of patients with LUTS secondary to BPH and warrant further study of the potential relationship between psychiatric symptoms and treatment response in these patients. Patients with BPH could be best managed using a multidisciplinary approach, including routine psychological assessment.

Future studies are needed to evaluate the relationship between depression and LUTS secondary to BPH. If a causative relationship exists, whether unidirectional or bidirectional, changes in current management of these patients might be warranted. For a speculative example, treatment for patients with BPH who are at risk for developing depressive symptoms might also be extended to include antidepressant medication.

This review suggests that a bidirectional association may exist between depression and LUTS secondary to BPH. However, many evaluated studies relied on a single survey instrument, included only small sample sizes over short follow-up periods, failed to note longitudinal changes, and lacked strong evidence of causality. Most previous studies focused on the relationship between BPH and the presentation of depressive symptoms, rather than focusing on a diagnosis for depressive disorder. Moreover, the degree to which depression in- fluences treatment and/or treat-ment response for LUTS secondary to BPH and vice versa is under-studied. Further evaluation is necessary. Finally, although several potential mechanisms underlying the association of depression and BPH have been postulated, robust data on pathophysiologic mecha-nisms are not available. Further study is needed to help identify patients at risk and develop novel therapeutic strategies. ■

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## MAIN POINTS

- Approximately half of men over 40 are diagnosed with benign prostatic hyperplasia (BPH). Of these men, approximately 50% will develop significant and bothersome lower urinary tract symptoms (LUTS) secondary to BPH. LUTS secondary to BPH is associated with decreased quality of life and may include urgency/frequency, incontinence, and nocturia.
- Depression plays a role in the pathogenesis of a number of chronic diseases, including inflammatory bowel disease, arthritis, asthma, and diabetes; a relationship has also been identified between depression and urologic diagnoses such as incontinence. Symptoms of BPH are associated with decreased quality of life and depression, and the literature strongly suggests that there may also be a pathophysiologic relationship between BPH and depression; in addition, depressive symptoms are also associated with treatments for BPH.
- Data have suggested a bidirectional relationship between depression and inflammatory disease states; this association could extend to LUTS secondary to BPH.
- The gold-standard surgical treatment for BPH is transurethral resection of the prostate. Side effects, which may include incontinence and erectile dysfunction (ED), may contribute to depression. ED has been found to be associated with increased rates of LUTS and depression.
- It is recommended that clinicians screen for depression in all patients presenting with LUTS suggestive of BPH, as well as for LUTS in patients presenting with depressive symptoms.

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