Psychiatr. Pol. ONLINE FIRST Nr 32
Published ahead of print 15 October, 2015
www.psychiatriapolska.pl
ISSN 0033-2674 (PRINT), ISSN 2391-5854 (ONLINE)
DOI: http://dx.doi.org/10.12740/PP/OnlineFirst/59162

Lower urinary tract symptoms, nocturia and overactive bladder in patients with depression and anxiety

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Summary

Lower urinary tract symptoms (LUTS) remain highly prevalent worldwide, and are well known to negatively impact patients' quality of life, sleep and psychosocial wellbeing. Conversely, both depression and anxiety have been shown to have a negative effect on perception, development and prolongation of LUTS. This paper provides an overview of an association between the lower urinary tract symptoms, depression and anxiety. It also explores possible common mechanisms underlying the causes of both conditions.

There has been a large body of evidence linking LUTS with anxiety and/or depression. Studies have documented not only a significant impact of LUTS on the psychosocial wellbeing, but also showed a strong negative effect of depression and anxiety on perception, development and prolongation of LUTS. High level of psychiatric morbidity has important implications on the appropriate management in patients with LUTS, as well as LUTS may have important implications on development and management of depression and anxiety. Therefore, clinicians should be aware of the bidirectional association between LUTS and anxiety and/or depression, as some patients may require a multidisciplinary approach and a combined treatment. The precise common mechanism underlying LUTS, depression and anxiety remain largely unknown and further research is needed to elucidate the underlying pathophysiological pathways.

Key words: lower urinary tract symptoms, depression, anxiety

Introduction

Lower urinary tract symptoms (LUTS) encompass storage (daytime urinary frequency, nocturia, urgency, urinary incontinence (UI)), voiding (hesitancy, straining, slow stream, intermittency, terminal dribble), and post-micturition symptoms (sensation of incomplete emptying, post-micturition dribble) [1]. LUTS are not disease or condition specific, and despite being commonly related to bladder outlet obstruction, LUTS may be indicative of bladder dysfunction and other structural and/or functional abnormalities of the urinary tract, as well as, they may herald many non-urological conditions [1, 2]. LUTS are particularly prevalent among adult men from the general population. In the Epidemiology Urinary Incontinence and Comorbidities (EPIC) study, which included a total of 19,165 adults from Canada, Germany, Italy, Sweden and the UK, an overall prevalence of LUTS was 62.5% in men and 66.6% in women aged ≥ 40 years [3]. In subgroup analysis 37.7% of all men reported having experienced only one LUTS subtype, whereas 24.8% reported having experienced more LUTS subtypes of which storage plus voiding LUTS (8.9% of the general population sample) were the most frequently reported LUTS cluster [4]. The Epidemiology of Lower Urinary Tract Symptoms (EpiLUTS) study, which was an internet-based population survey in Sweden, the USA and the UK, reported prevalence of at least one LUTS of at least "sometimes" frequency in 72.3%, and 76.3% of men and women, respectively [5]. Similarly, other studies have confirmed that LUTS are highly prevalent and costly condition worldwide [6].

Despite not being considered life threatening, numerous studies have demonstrated that LUTS exhibit a negative impact on health-related quality of life (HRQL), sleep, as well as on physical and mental health [5, 7–9].

Association of lower urinary tract symptoms with anxiety and depression

Anxiety and depression are a very common group of disease, with an overall prevalence of 2–16.5% [10–13]. Depression, which is expected to become the second leading cause of disease burden by 2020, plays an important role in the pathogenesis of numerous chronic conditions [14, 15]. A relationship between anxiety, depression and the LUTS has been the topic of many reports over the last few decades, with the first one describing this association in 1964 [16]. Several more recent and larger studies have investigated this link in a prospective manner. A large cohort study carried out on 1,980 Chinese men of 65 to 92 years of age, showed a significant association between moderate-to-severe LUTS and clinically relevant depressive disorders [17]. Importantly, a dose–response relationship was observed between mounting LUTS severity and increasing risk of clinically relevant depressive symptoms. Further corroborating data came from the Androx Vienna Municipality Study, which investigated LUTS and depression in a homogenous cohort of 673 healthy men, and found a significant association between these two symptom complexes [18]. Similarly, findings from the

EpiLUTS, a large observational longitudinal, multicentre study, which included 30,000 adult subjects, confirmed the negative effect of LUTS on the HRQL, and reported high level of anxiety and depression, with 35.9% of men and 53.3% of women meeting self-reported screening criteria for clinical anxiety (Hospital Anxiety and Depression Scale (HADS) score ≥ 8), and 29.8% of men and 37.6% of women meeting self-reported criteria for clinical depression (HADS ≥ 8) [7]. In a further sub-analysis of EpiLUTS, men with mixed urinary incontinence had the highest rates of clinically relevant anxiety (42.1%) compared to other types of UI [19]. However, in women, stress incontinence was predominantly associated with anxiety (49.7%), and depression (34.9%). Deleterious impact of LUTS on emotional wellbeing has also been shown in the EPIC study, a large, cross-sectional survey in Canada, Sweden, Germany, Italy, and the UK [20]. In nested control analysis presence of LUTS was significantly associated with depression compared to controls, with symptoms in three LUTS groups (overactive bladder syndrome (OAB), post-micturition and voiding symptoms) having the greatest impact on rate of depression. Further corroborating evidence of relationship between LUTS and anxiety and depression came from a recent study in Taiwan [21]. Data from a random population sample of enrolees in the National Health Insurance Programme in 2001–2009, consisted of 22,980 LUTS patients, and 45,960 matched controls. The results showed that patients with LUTS had a significantly higher prevalence of anxiety or depression than matched controls (11.5% versus 5.7%). After controlling for sociodemographic variables and other major systemic diseases, the odds ratios for anxiety, depression, either anxiety or depression, and both anxiety and depression, were 2.05; 2.19; 2.14 and 2.56, respectively.

Chances of depression causing LUTS were also subject to many investigations [20, 22–26]. The Boston Area Community Health (BACH) survey, a community-based epidemiologic survey, found that LUTS were significantly associated with depression, and that depression increased the odds of LUTS. Recently, an interesting report has been published. It examined the association of LUTS with suicidal ideation in 2,890 men from the National Health and Nutrition Examination Survey (NHANES), who were 40 years old or older [27]. Data from this cross-sectional study showed that men with more LUTS were more likely to have depression and suicidal ideation. Moreover, men with greater depression scores (the Patient Health Questionnaire-9 (PHQ-9) score ≥ 5, and ≥ 10 were used as a threshold for identifying the outcome of moderate and major depression, respectively) were more likely to suffer from LUTS. Based on the findings from the aforementioned studies a bidirectional nature of relationship between LUTS and the affective disorders should be considered.

The association between LUTS and anxiety and depression could be attributable to several different mechanisms. LUTS reduce HRQL, and can lead to embarrassment, social anxiety, demoralisation, and poor self-esteem [27]. Moreover, having LUTS may be perceived by the patients themselves, as well as their partners and family as a sign of weakness and aging [28]. Further, nocturia and disturbed sleep both result in daytime drowsiness, inability to concentrate and subsequent anxiety [29–31]. As a consequence

of this significant emotional distress related to LUTS, affective disorders may develop [32]. In addition, it has been suggested that stress accompanied by anxiety and/or depression may be an important factor contributing to the development and prolongation of LUTS [33]. Moreover, some antidepressants and anxiolytics have been suggested as the risk factors for LUTS [34]. Other possible mechanisms explaining coexistence of LUTS with depression and anxiety involve altered concentration of serotonin and norepinephrine in the central nervous system (CNS) in patients with LUTS, as well as, in those with anxiety and depression [35, 36]. Furthermore, increased adrenergic tone and the hypothalamic-pituitary axis have been proposed to mediate the depressive symptoms and LUTS. [37]. Finally, inflammation, which has been involved in the pathogenesis of both LUTS and depression, may also play a role [38, 39].

Nocturia, depression and anxiety

Nocturia is defined by the International Continence Society (ICS) as the complaint that individual has to wake at night one or more times to void; each void is preceded and followed by sleep [40]. It affects a large proportion of adults and is one of the most frequently reported lower urinary tract symptom [1, 3]. In the EPIC study, an overall prevalence of nocturia was 54.5% in women and 48.6% in men [3]. The prevalence increased with age in both sexes and ranged from 34.5% and 43.9% in younger (≤ 39yeras old) men and women, respectively, to 71.9% and 70.8% in older (≥ 60 years old) male and female individuals, respectively. Data from the National Sleep Foundation telephone pole conducted in a representative sample of 55–84 years old Americans obtained similar results with 53% of subjects reporting nocturia [41]. Notably, in this study nocturia was over four times as frequently as the next most often cited cause of poor sleep, the pain. More recent data from a cross-sectional telephone survey conducted in general population from five European countries on 22,740 non-institutionalised individuals aged 15 or over, also indicated that nocturia remains an important cause of insomnia [42].

Nocturia may be the symptom of some primary urological disorders including benign prostatic hyperplasia, benign prostatic enlargement or OAB, or may be related to heart disease, hormonal imbalances, sleep problems and lifestyle factors [1]. Regardless the cause, repeated fragmentation of sleep results in daytime drowsiness, poor concentration and anxiety which adversely affects occupational functioning, physical and emotional health, as well as, patient's quality of life [29–31]. Moreover, nocturia can also lead to embarrassment and poor self-esteem [43, 44]. In result, it may increase the risk of depression. This link was first described by Asplund et al. in 2004 [45]. In this study, conducted in an unselected group of 1,375 adults from Sweden, major depression was associated with a six-fold increase of nocturia in men, and a three-fold increase in women, after accounting for age and somatic health. In the BACH study, which investigated the association of nocturia with QoL and depressive symptoms in 5,203 men and women, the risk of depressive symptoms

in men with nocturia was 2.79 (95% confidence interval (CI): 1.81–4.31), whereas in women 1.80 (95% CI:1.29–2.51) [46]. Similarly, several other cross-sectional studies confirmed the association of nocturia with depression [30, 43, 45–51]. A recent systematic review on the relationship of depression and anxiety with nocturia, reported that waking up at night to void increased the odds of reporting depression from 1.2 to 20.24 [23].

Possibility of depression to cause nocturia was also subject to few investigations and the reported odds were from 1.2 to 7.73 [23, 43]. An elegantly designed prospective cohort Tampere Aging Male Urologic Study (TAMUS) from Finland assessed the effects of depressive symptoms on the incidence of nocturia in 1,580, 50–70-years old men followed for 5 years [44]. The results showed that the individuals with depressive symptoms at study entry were at 2.8 times higher risk (95% CI: 1.5–5.2) for moderate or severe nocturia than those without depressive symptoms. Of note, a dose-response relationship was found between the severity of depressive symptoms at baseline and the incidence of moderate or severe nocturia. However, nocturia at baseline had no significant effect on the odds of depressive symptoms during follow-up.

In TAMUS study, antidepressants or antipsychotic medications did not appear to increase the nocturia incidence rate (relative risk (95% CI), was 0.7 (0.4–1.4), and 1.1 (0.4–3.0) for mild, and moderate or severe nocturia, respectively). However, effects of selective serotonin reuptake inhibitors (SSRIs) on nocturia remain unclear. Although antidepressants have not been shown to affect day-to-night urine production ratio in some studies [44, 52], in a report by Asplund et al., SSRIs use doubled the risk of two or more nocturnal voids in both men and women [53].

An association of nocturia with anxiety has been investigated to much smaller extent than that with depression. The EpiLUTS study linked nocturia to clinically relevant anxiety (HADS score ≥ 8) in both men and women [7]. Similar results were published by another group [54].

The findings from aforementioned studies suggest that an association between nocturia and anxiety and depressive symptoms may be bidirectional in nature. However, as the level of evidence is 2 at its best (according to the Oxford Centre for Evidence-based Medicine classification), there is a need for further, well-designed studies that will clarify the exact nature of these associations [55].

Although the exact mechanisms that might explain a relationship between depression, anxiety and nocturia remain unknown, several shared pathophysiological pathways may need to be considered. Depressed patients have higher overall level of antidiuretic hormone (ADH) than healthy controls [56]. However, they lack normal rise in the ADH level. Consequently the loss of circadian rhythm of circulating ADH may contribute to nocturia [45]. Such abnormality is also a common mechanism of nocturnal polyuria in adult and elderly people [57, 58].

Another possible explanation may be a negative effect of sleep fragmentation and other causes of disturbed sleep on the nocturnal urine output. It has been shown that during sleep the urine output is lower than while awake [59, 60]. Of note, in depressed

patients insomnia is common [61]. Therefore, it seems possible that nocturia-related sleep disruption may lead to depression.

Further proposed mechanism linking affective disorders with nocturia involve altered concentration of serotonin and norepinephrine in the CNS [35, 36]. In rats, lowering serotonin levels in the CNS resulted in depression and overactive bladder [62, 63]. However, administration of serotonin reuptake inhibitors, as well as serotonin receptor agonists depressed reflex bladder contractions and increased the bladder volume threshold for inducing micturition [63].

Overactive bladder, depression and anxiety

Overactive bladder is defined by the International Continence Society as the presence of urinary urgency, usually accompanied by frequency (voiding 8 or more times in a 24-hour period) and nocturia (awakening at night to void), with or without urgency urinary incontinence, in the absence of UTI or other obvious pathology [40]. In general population, OAB prevalence rates range from 7% to 27% in men, and 9% to 43% in women, and tend to increase with age [3, 64, 65]. A number of population-based studies have reported the effect of OAB on HRQL [65]. Similarly, the relationship between OAB and affective disorders has been subject to many investigations [7, 66, 67].

Although a large body of evidence has supported a positive association of OAB and depression, a link between anxiety and OAB has been documented less extensively. A recent systematic review on affective symptoms and the overactive bladder, found that only six out of nine studies identified a positive relationship between OAB symptoms and anxiety, three showed no association, and two case-control studies reached contradictory conclusions [66].

The effect of OAB symptoms on anxiety and depression was observed in EpiLUTS study [7]. This cross-sectional population-representative survey was conducted on 30,000 participants from the USA, the UK and Sweden who rated their LUTS, condition-specific health related quality of life, generic health status, anxiety and depression (using HADS). In this study, OAB symptoms were markedly associated with positive HADS anxiety sub-scores. Data from the US EpiLUTS study not only has confirmed this observation, but it also identified patients with bothersome OAB symptoms to be the group more likely to report anxiety than that with OAB without bothersome symptoms [67]. Similar results provided the European part of the EpiLUTS study [68]. English and Swedish men and women with bothersome OAB were significantly more likely to seek treatment, report the lowest levels of HRQL and work productivity and the highest levels of anxiety and depression compared to those with no or minimal symptoms and OAB without bother. Moreover, greater severity of urgency, urgency urinary incontinence, frequency, nocturia, and increasing levels of anxiety were strongly predictive of OAB bother. These results may suggest a bidirectional relationship between overactive bladder and anxiety. However, more evidence is still required.

A relationship between depression and OAB has been much better documented than between anxiety and OAB. Based on cross-sectional cohort, as well as, randomised controlled studies it seems plausible that this association is bidirectional in nature. The National Overactive Bladder Evaluation (NOBLE) Programme, a telephone survey, was initiated to assess the prevalence and the impact of OAB in 5,204 English-speaking adults in the USA [24]. The results showed that OAB with and without urge incontinence was associated with higher the Centre for Epidemiologic Studies Depression Scale (CES-D) scores in both men and women than the OAB-negative controls. Additional sub-analysis limited to the 919 participants in the nested case-control study with 171 reporting urge, stress or mixed incontinence, confirmed presence of depressive symptoms (CES-D > 16) in all the incontinence groups. No significant differences regarding depression severity between incontinent subjects were found [3]. Another evidence supporting association of OAB symptoms with depression comes from the EPIC study [20, 25]. Of the EPIC participants, 1,434 identified cases of OAB were matched by age, gender and country with 1,434 controls. The nested case-controlled analysis revealed that depression with CES-D $\geq$ 21 was statistically more common in those with OAB (regardless of associated incontinence) than in controls (148 versus 46 individuals, respectively, $p < 0.001$) [25]. Further corroborating evidence of positive relationship between OAB symptoms and depression was provided by the participants from the EpiLUTS study. Those respondents to the survey questions who were bothered by OAB symptoms were more likely to report depression than individuals not reporting bother [19, 66, 68]. Interestingly, the respondents with OAB had a higher rate of anxiety (31%), and depressive symptoms (27%) compared to the rates from other cross-sectional reports [19, 24, 25, 69].

Many other investigators also linked depression with OAB [69–72]. However, the NOBLE, EPIC and EpiLUTS studies reported on the co-occurrence of OAB and depression, whereas a new onset of OAB in men and women with depression was reported in four studies [20, 24, 50, 73–75], and a new onset of depression in OAB patients was delineated by others [73, 74]. A bidirectional nature of this relationship seems therefore very likely.

Important data regarding OAB treatment-related modulation of the depressive symptoms comes from a randomised, multicentre controlled trial in a cohort of men with OAB by Staskin et al. [76]. In this study, all participants received oxybutynin patch for overactive bladder symptoms. The proportion of men with the Beck Depression Inventory-II (BDI-II) score > 12 (indicating depression) decreased from 23.9% to 17.9% after 6-month treatment period ($p = 0.0055$).

The association between OAB, depression and anxiety could be attributed to several mechanisms. Firstly, patients bothered by OAB symptoms have poor health-related quality of life [20, 76]. Secondly, OAB can have a considerable effect on daily activities and negatively affect self-esteem, which consequently may lead to anxiety and depression [20, 77]. In addition, OAB may also affect patients' mood indirectly by its negative impact on the quality of sleep [75, 78]. Moreover, it is possible that

stress associated with anxiety and/or depression may be a factor in the perception and development of OAB [33]. The association between OAB and anxiety or depression, may further be explained by the fact that these syndromes share common biological pathways. Some studies have shown that serotonin and norepinephrine are involved in the pathophysiology of anxiety and depression [35, 36]. In animal experiments, lowering serotonin levels in the CNS resulted in both hyperactivity of the bladder, and depressive symptoms [62, 63]. However, administration of SSRI, fluoxetine, reversed the urinary symptoms [79]. Similarly, in humans, administration of a serotonin and norepinephrine reuptake inhibitor (SNRI), duloxetine, led to significant improvements of symptoms in adult female patients with OAB compared with placebo group [80].

A neuro-endocrine explanation for association of OAB symptoms with depression and anxiety may be found in shared dysregulation of the hypothalamic–pituitary-adrenal axis, which plays a role in depression and anxiety disorders [81]. In addition, corticotrophin-releasing factor (CRF), a neuropeptide which acts within both the brain and the periphery to coordinate the overall response of the body to stress has been shown to have an inhibitory effect in the pontine-spinal pathway and lower micturition threshold and urine volume in an animal model [82, 83].

Another possible explanation linking OAB with depression and anxiety refers to the deleterious changes in the limbic system. The anterior cingulate cortex (ACC) is involved in autonomic emotional and motor arousal and in monitoring [84]. Moreover, the areas in the right anterior cingulate gyrus and the right inferior frontal gyrus are involved in voluntary voiding of healthy males [85]. It has been shown that dysfunction of the limbic system and hypoperfusion, especially in the anterior cingulate cortex, may be implicated in late-life depression in female patients [86]. In addition, genuine urge incontinence with reduced bladder filling sensation was associated with global hypoperfusion of the frontal areas of the brain in geriatric patients [85], and reduced anterior cingulate cortex activity accompanied by failure of inhibition of detrusor overactive contractions [87].

Conclusions

There has been a large body of evidence linking LUTS with anxiety and/or depression. Studies have documented not only a significant impact of LUTS on the psychosocial wellbeing, but also showed a strong negative effect of depression and anxiety on perception, development and prolongation of LUTS. High level of psychiatric morbidity has important implications on the appropriate management in patients with LUTS, as well as LUTS may have important implications on development and management of depression and anxiety. Therefore, clinicians should be aware of the bidirectional association between LUTS and anxiety and/or depression, as some patients may require a multidisciplinary approach and a combined treatment. The precise common mechanism underlying LUTS, depression and anxiety remain largely unknown and further research is needed to elucidate the underlying pathophysiological pathways.

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