

# Diagnosis, Evaluation, and Treatment of Mixed Urinary Incontinence in Women

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Mixed urinary incontinence (MUI) is a common clinical problem in the community and hospital setting. The broad definition of the term makes it difficult to diagnose, as well as determine effective treatment strategies. There are no current guidelines recommended for physicians. The estimated prevalence of this condition is approximately 30% in all women with incontinence. It has also been suggested that patients with MUI report more bothersome symptoms than either stress or urge incontinence; approximately 32% of 40- to 64-year-olds with MUI report symptoms of depression. The authors examine the diagnosis, evaluation, and treatment of patients with MUI.

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## KEY WORDS

Mixed urinary incontinence • Detrusor overactivity • Stress incontinence • Urge incontinence • Urodynamic stress incontinence • Pelvic organ prolapse • Transvaginal tape

**M**ixed urinary incontinence (MUI) is the leading cause of incontinence in the community and hospital setting.<sup>1</sup> The term refers to a combination of symptoms, with the patient exhibiting features of both stress urinary incontinence (SUI) and urge urinary incontinence (UUI); it may also refer to a combination of features of urodynamic SUI and detrusor hyperactivity.<sup>1</sup> The current International Continence Society guidelines define MUI as a complaint of the involuntary loss of urine during exertion, sneezing, or coughing, as well as leakage associated with urgency.<sup>2</sup>

The term MUI is extremely broad because it may refer to equal stress and urge symptoms, stress-predominant symptoms, urge-predominant symptoms, urodynamic SUI (USUI) with detrusor overactivity (DO), or USUI with clinical urge symptoms but no DO.<sup>3</sup> The challenge of this broad definition is that it leads to inconsistencies when evaluating treatment options and outcomes. In an attempt to validate diagnostic questions that could later be used in an epidemiological survey, Sandvik and colleagues<sup>4</sup> defined MUI based on subjective answers to a structured questionnaire designed for

their study.<sup>4</sup> SUI was presumed if a positive answer was given to the question: “Do you lose urine during sudden physical exertion, lifting, coughing, or sneezing?” If the patient responded positively to the question: “Do you experience such a strong and sudden urge to void that you leak before reaching the toilet?” then a diagnosis of UUI was presumed. MUI was considered if a positive answer was

MESA and UDI questionnaires in 551 women with a mean age of  $56 \pm 16$  years. They estimated a prevalence rate of 30% of MUI in all women with urinary incontinence.

According to Dooley and associates,<sup>7</sup> in their cohort, MUI was more bothersome to patients than either pure SUI or UUI. In a cross-sectional population-based study across 6 European countries that included over 300 patients,

life, and history of previous pelvic or vaginal surgery. Multiple validated tools exist for the initial evaluation including the Questionnaire for Urinary Incontinence Diagnosis, as well as the Stress/Urge Incontinence Questionnaire. These questionnaires are used both to record symptoms and to assess treatment benefits.<sup>9</sup>

Physical examination is the next step in a patient’s evaluation. It includes a general, abdominal, and pelvic examination. The determination of the body mass index (BMI) of the patient is an important modifiable risk factor for the development of incontinence.<sup>10</sup> The abdominal examination focuses on checking for masses that may be present; pelvic examination should include evaluation of urethral mobility, pelvic organ prolapse, and urogenital atrophy. In addition, assessment of the

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given to both questions. In contrast, Brubaker and colleagues<sup>5</sup> reported that strict definitions based on self-reported symptoms do not properly categorize patients as having MUI. Their group believed that patients should be broken down into MUI subgroups of SUI and UUI rather than describing it as a single entity. However, without a precise definition or understanding of the role of these stress and urge subcomponents, the assessment of an intervention for SUI or UUI is challenging.<sup>6</sup>

The prevalence rates of MUI vary widely in the literature. In a secondary analysis of the Stress Incontinence Surgical Treatment Efficacy Trial (SISTeR), Brubaker and colleagues<sup>5</sup> evaluated 655 women for the presence of incontinence and their response to treatment. They found that 50% to 93% of women fell into the category of MUI based on patient-reported answers to the Medical Epidemiologic and Social Aspects of Aging (MESA) and Urinary Distress Inventory (UDI) questionnaires. However, when objective criteria such as urodynamic findings were used, only 8% of women were categorized with MUI. Dooley and associates<sup>7</sup> compared physical examination findings and responses to the

the effects of overactive bladder (OAB) symptoms on employment, social interactions, and emotional well-being were evaluated by direct interview or a telephone-conducted interview. Irwin and associates<sup>8</sup> found 32% of patients aged 40 to 64 years reported being depressed. In addition, they determined

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that symptoms of OAB have a statistically significant negative impact on emotional well-being both at home and at work.

We sought to examine the existing literature on MUI and better understand the role urodynamic testing (UDS) plays in its diagnosis. In addition, we sought to examine treatment methods so that better treatment outcomes may be achieved.

## Evaluation and Diagnosis

Assessment of patients with MUI begins with a thorough history of the patient’s urinary symptoms. This includes onset and timing of stress and urge symptoms, history of any urinary tract infections or sexually transmitted diseases, an obstetric history, bowel function, a frequency-volume diary, symptom questionnaires, effects on quality of

pelvic muscle floor tone is important,<sup>11</sup> as this could be a sign that SUI is present. Urinalysis and urine cultures are valuable tests in the initial evaluation to rule out an infection. Determination of postvoid residual urine volume is important because an elevated volume may exacerbate both SUI and UUI.

UDS may be a useful tool in determining the patient’s primary type of incontinence. American Urological Association (AUA) and Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction guidelines for the use of urodynamics in MUI give the physician much leeway in deciding whether to use it or not. Although they admit that the study may not predict outcomes for treatment, they state that it may aid in correlating symptoms. In addition, they

recommend that physicians counsel patients that the absence of DO in the study results does not exclude MUI as the cause of their symptoms.<sup>12</sup> Chaliha and Khullar<sup>13</sup> reported in their study that up to 50% of patients with UI do not have DO on testing, and not all women with SUI leak during testing.<sup>13</sup> Digesu and coworkers<sup>3</sup> reported that it may fail to identify DO in up to 40% of women with MUI. Conversely, guidelines for the use of urodynamics proposed by the European Association of Urology and AUA suggest that findings consistent with DO can

## Pathophysiology

The pathophysiology of MUI is complicated because of the intertwining of SUI pathophysiology and UI pathophysiology. MUI involves several factors that may be responsible for its development, including striated muscle atrophy, disturbances in estrogen deficiency, abnormalities in histomorphology, and microstructural changes.<sup>15</sup> Several other biochemical processes that may be responsible for its development include decreased vaginal collagen content,

urethra, and may act as a stimulus to aggravate or possibly initiate detrusor hyperactivity.<sup>19</sup> In a study by Mahony and colleagues,<sup>20</sup> in which they examined various reflexes involved in micturition, it was found that urine flow across urethral mucosa led to an increase in the excitability of the micturition reflex. Barrington<sup>21</sup> determined that distention of the proximal urethra or water running through the urethra caused contraction of the detrusor muscle in cats. Ultimately, it is likely that one theory or risk factor does not explain the development of MUI and its symptoms; it is more probable that disturbances in several elements and the inability of the bladder to compensate result in the development of MUI.<sup>15</sup>

*It is unclear what benefit, if any, UDS testing may provide for patients and clinicians in helping to guide treatment.*

greatly influence treatment options and outcomes.<sup>10,12</sup> It is unclear what benefit, if any, UDS testing may provide for patients and clinicians in helping to guide treatment. All of these studies challenge the usefulness of UDS in the setting of MUI.

As mentioned previously, the challenge in using UDS testing is that, in many cases, the test does not show findings that match the patient's symptoms and is, therefore, inconclusive. In a clinical sample of 950 patients, Weidner and coworkers<sup>14</sup> reported that 52% of patients reported symptoms of MUI; however, only 14% were found to have MUI verified by urodynamic evaluation. Sandvik and colleagues<sup>4</sup> reported on similar findings in their study of 236 women. At the time, 46% of patients presented with symptoms of MUI, but only 44% of those patients were given the diagnosis of MUI by a physician based on clinical history, physical examination findings, and urodynamic evaluation. This leads to the assumption that the use of UDS is less than reliable in determining a diagnosis.

increased vaginal messenger RNA matrix metalloproteinase, and increased collagen breakdown.<sup>16</sup> Jung and coworkers<sup>17</sup> examined the effects of stimulation of urethral afferent nerves on reflex detrusor contraction by studying animal models. They determined that women with USUI may have an incompetent sphincter and bladder neck, which allows urine to enter the

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proximal urethra during physical exertion or Valsalva maneuver, causing a urethra-detrusor reflex that triggers an involuntary detrusor contraction, which then causes urgency and UI. Urine flow, during micturition, is regulated by the nervous system and involves the muscles of the bladder base, proximal urethra, and external urethral sphincter to induce urethral relaxation. In a healthy patient, urine only enters the urethra during micturition<sup>18</sup>; however, in patients with incontinence, urine is constantly present in the

## Treatment

Treatment for MUI is generally based on the predominant symptom that the patient reports as being the most bothersome.<sup>5</sup> Multiple treatment modalities exist, including conservative treatment,

and pharmacologic and surgical options.

### Conservative

Conservative therapy should be considered as first-line therapy for MUI patients. Goals include correction of voiding patterns, improvement in the ability to suppress urge, and increase in bladder capacity and continence. Therapy includes lifestyle interventions, bladder retraining, anti-incontinence devices, biofeedback, and pelvic floor muscle exercises. Obesity is an important modifiable risk factor, and weight loss for improvement of

symptoms is supported by Level 2 evidence in morbidly obese patients and Level 1 evidence in moderately obese patients.<sup>15</sup> In a randomized controlled trial of 338 overweight and obese women  $\geq 30$  years with a BMI between 25 and 50—many of whom suffered from MUI as determined by answers to questions routinely used by the investigators as well as medical histories—Subak and associates<sup>22</sup> demonstrated that women who participated in a 6-month weight loss and behavioral modification program had a reduction of  $\geq 70\%$  in frequency of all types of incontinent episodes ( $P < .001$ ). This represented a significantly higher proportion of patients as compared with the control group. Although not

in median incontinent episode frequency at 40 mg/d (62% and 58%, respectively) and 80 mg/d (63% and 65%, respectively) of duloxetine compared with placebo (33% and 44%, respectively; all  $P < .05$ ). In a similar study performed by Bent and associates,<sup>24</sup> 588 women with MUI were randomized to either 80 mg/d of duloxetine therapy or placebo. Overall, incontinence episode frequency was decreased significantly with the use of duloxetine.

Evidence also supports the use of antimuscarinic therapy in the use of MUI. Khullar and coworkers<sup>25</sup> performed the first randomized, controlled clinical trial of tolterodine, an antimuscarinic agent, for the treatment of MUI. The

efficacy and safety; 520 men and women with a history of OAB, UUI, or MUI, were randomized to treatment. During the double-blind treatment period, patients treated with 3.9 mg of transdermal oxybutynin had a significant ( $P = .0165$ ) reduction in the number of incontinence episodes per week from baseline to the study end, as compared with the placebo-treated group. The significance in the therapeutic effect was evident by the third week of treatment and was maintained throughout the double-blind period.<sup>26</sup>

### *Surgery*

In women with predominant symptoms of SUI, surgery may be an effective form of treatment, as it is the mainstay of treatment of SUI. Surgical options include retropubic colposuspension (Burch procedure), pubovaginal sling, and tension-free transvaginal tape (TVT). Gamble and colleagues<sup>27</sup> reported on 305 women with MUI who were treated with transobturator retropubic or bladder neck sling. The use of the transobturator sling was reported to have the lowest rate of persistent

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statistically significant, the results were clinically significant. The authors suggested that overweight and obese women may benefit from a weight-loss program for the improvement of their incontinence. Pelvic floor muscle training has also shown to improve symptoms of patients. Cavkaytar and colleagues<sup>23</sup> found that 41.2% of women with MUI in their study had significant improvement of their symptoms following a home-based Kegel exercise program.

### *Pharmacologic*

Several studies have reported on the positive benefits of both anti-muscarinic and serotonin-norepinephrine reuptake inhibitor (SNRI) drug therapy. Bump and colleagues<sup>1</sup> performed a double-blind, randomized controlled trial on the treatment response to duloxetine, a selective SNRI, versus placebo. Patients in the MUI and SUI groups had significant decreases

study consisted of 854 women, aged  $\geq 18$  years, with urge-predominant MUI as determined by the clinician. A decrease in the number of weekly UUI episodes compared with placebo treatment was statistically

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significant after 1 week of treatment ( $P = .0009$ ) and after 8 weeks of treatment ( $P < .0001$ ). In addition, the number of micturitions per 24 hours, the number of urgency episodes per 24 hours, and the volume voided per micturition improved to a greater extent in patients receiving tolterodine than in those patients in the placebo group. Dmochowski and associates<sup>26</sup> conducted a double-blind, randomized controlled study in which three doses of oxybutynin were delivered transdermally, followed by a 12-week open-label dose-titration period to assess

DO, demonstrated by postoperative UDS. In a prospective long-term study of 80 women with a mean age of  $59 \pm 11$  years and a mean parity of 2, Rezapour and Ulmsten<sup>28</sup> found a subjective cure rate in 85% of patients with MUI following TVT use. Paick and colleagues<sup>29</sup> evaluated a total of 144 women on the outcome of MUI following TVT, suprapubic arc sling, or transobturator tape procedures. Similar cure rates were found in all three groups for SUI (96%, 90%, and 94%, respectively) and UUI (82%, 86%, and 82%, respectively).<sup>29</sup> Cure of SUI and UUI were both determined by the

absence of subjective complaints of leakage; in addition, the cure for SUI was also determined by the absence of objective leakage on stress testing. All cases that did not meet the criteria for cure were considered treatment failure. Paick and colleagues<sup>29</sup> also found an increased chance of treatment failure of UUI when low maximum urethral closing pressure and DO were present preoperatively on UDS.

UDS has been used as a tool to predict treatment outcomes. The effect of urodynamic intrinsic DO

sling placement was 40.3% and 32.3%, respectively.<sup>32</sup> The study found that preoperative SUI in combination with DO was an independent risk factor for the continued presence of urgency and UUI symptoms.

The determination of treatment outcomes by UDS in those patients who will not undergo surgical interventions is not as clear. Burgio and colleagues<sup>33</sup> determined that urodynamic parameters were not predictive of outcome in either pharmacologic therapy or

of other treatment options or reinterventions.

### Conclusions

The definition of MUI comprises a large number of patients, which makes it a challenging condition to study. Given the wide variety of patients with the diagnosis, a better definition or re-evaluation of the term MUI needs to be established. Improving an objective classification system is one approach that can be used because the use of subjective, symptom-only criteria is inconsistent.

UDS has not been shown to be of benefit in the diagnosis of MUI. However, its use in determining treatment outcomes may be beneficial. Future studies should focus on the development of instruments to properly classify patients. These instruments should be able to separate urge and stress symptoms and assess the magnitude of their effects on overall symptoms. Whereas UDS is unable to classify patients, or to predict their response to treatment, newer instruments may be able to do so and allow for the comparison of trial outcomes.

Initial treatment of a patient with MUI should include weight loss when necessary, as well as the use of pelvic floor exercises. When conservative treatment options fail, evidence suggests that the use of

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on treatment outcome has mainly been examined in patients following surgical interventions. In addition, several preoperative urodynamic parameters have been studied for their ability to predict outcome, specifically, if OAB symptoms will resolve following sling placement.<sup>30</sup> In a retrospective study conducted by Panayi and colleagues, 51 women who had symptoms of SUI and urodynamic findings of OAB were treated with TVT.<sup>31</sup> It was found that a significantly higher preoperative opening detrusor pressure was present in patients with persistent postoperative symptoms of OAB than in those patients without these symptoms. Therefore, the conclusion was made that a high preoperative opening detrusor pressure may be predictive of postoperative intrinsic DO after TVT implantation in women with MUI. In a large observational cohort study that included 1225 women  $60.6 \pm 12.8$  years who underwent midurethral sling implantation, 62% of women reported symptoms of urgency or UUI. The overall rate of persistent urgency and UUI symptoms following midurethral

behavioral modification. Their recommendation is that women with MUI undergo UDS based on the physician's clinical judgment.

One question that remains is whether outcomes in women having anti-incontinence surgery are worse in those with an urge component than in those with pure SUI. Holmgren and colleagues<sup>34</sup> conducted a survey of 760 women who had undergone TVT surgery 2 to 8 years previously. In women with pure SUI, persistent cure rates of 85% were found 2 to 8 years following the procedure. In women with MUI, a persistent cure rate of 60% was found up to 4 years

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postoperatively, which steadily declined to 30% from postoperative years 4 to 8. This study suggests that, although women with pure SUI fare well when treated surgically, patients with urge components have a worse overall treatment outcome immediately after and several years postoperatively. These patients are therefore in pursuit

pharmacologic treatment with SNRIs or antimuscarinic therapy may be beneficial, especially in patients in whom urge-predominant symptoms are present. In contrast, surgical therapy is proven to be beneficial in patients with stress-predominant symptoms. However, the presence of de novo UUI or worsening UUI

following surgical treatment makes this treatment option less reliable for patients with MUI. ■

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## MAIN POINTS

- Mixed urinary incontinence (MUI) is a common clinical problem in the community and hospital setting. The estimated prevalence of this condition is approximately 30% in all women with incontinence. It is difficult to diagnose, as well as to determine effective treatment strategies, as there are no current recommended guidelines for physicians.
- MUI refers to a combination of symptoms, with features of both stress urinary incontinence (SUI) and urge urinary incontinence. It may also refer to a combination of features of urodynamic SUI and detrusor hyperactivity. The term MUI may refer to equal stress and urge symptoms, stress-predominant symptoms, urge-predominant symptoms, urodynamic SUI (USUI) with detrusor overactivity, or USUI with clinical urge symptoms but no detrusor overactivity.
- Assessment of patients with MUI begins with a thorough history of the patient's urinary symptoms and physical examination, which includes a general, abdominal, and pelvic examination. Pelvic examination should include evaluation of urethral mobility, pelvic organ prolapse, and urogenital atrophy.
- Conservative therapy should be considered as first-line therapy for MUI patients. Therapy includes lifestyle interventions, bladder retraining, anti-incontinence devices, biofeedback, and pelvic floor muscle exercises.