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OBM Geriatrics

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Review

Screening and Treating Urinary Incontinence in Primary Care: A Missed Opportunity

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Academic Editors: Ron J. Jankowski, Chi Chiung Grace Chen and Michael B. Chancellor

Special Issue: Incontinence Among Older Adults

OBM Geriatrics
2023, volume 7, issue 4
doi:10.21926/obm.geriatr.2304252

Received: May 12, 2023
Accepted: September 27, 2023
Published: October 05, 2023

Abstract

More than 60% of adult women in the United States have urinary incontinence (UI), with the prevalence increasing to over 80% in women over age 65. Despite its high prevalence, most patients do not seek care and few clinicians screen for UI. The Medicare Health Outcomes Survey queries patients about satisfaction with their provider's discussion and management of UI, but formal recommendations about screening, diagnosis, and treatment are lacking. This review presents a practical algorithm for primary care providers to incorporate management of UI into routine preventive care for women, and outlines UI prevalence, risk factors, screening, and non-surgical treatment options.

Keywords
urinary incontinence; stress incontinence; urge incontinence; mixed incontinence; functional incontinence; screening; treatment; algorithm; primary care; female

1. Introduction

Urinary incontinence (UI) is the involuntary loss of urine [1], and in women is often classified as stress, urgency, or mixed incontinence. Stress urinary incontinence (SUI) is the loss of urine on effort, physical exertion, sneezing, or coughing; urgency urinary incontinence (UUI) is the loss of urine associated with an overwhelming sense of urgency; mixed urinary incontinence (MUI) includes both SUI and UUI symptoms [1]. More common with aging is functional incontinence, or disability-associated UI, which may be due to a physical or cognitive condition that prevents a person from getting to the toilet in time to urinate [2]. Overflow incontinence resulting from urinary retention is uncommon in women.

1.1 Prevalence

A recent study analyzing data from the 2015-2018 National Health and Nutrition Examination Survey found the overall prevalence of UI in adult women in the United States (US) to be 62%, corresponding to 78,297,094 adult US women, reflecting an increase from previous estimates of 38-53% [3-6]. The prevalence of UI increases with age and ranges from 80-83% among women aged 65 years and older. Among women with UI, the most common type is SUI (38%), followed by MUI (31%) and UUI (22%), with 9% having unspecified incontinence (leakage that is not SUI or UUI). Incontinence costs related to supplies, laundry, and dry cleaning may reach $900-$4,000 annually for women with severe UI symptoms [7, 8].

1.2 Risk factors

Increasing age, especially greater than 70 years, increasing body mass index (BMI), especially greater than 40 kg/m^2, and a history of any vaginal birth have the greatest associations with UI [3]. The prevalence of UI increases with age even among nulliparous women [9, 10]. UI is often part of a geriatric syndrome including falls and cognitive impairment. Risk factors for developing UI in older adults include functional impairment, impaired mobility, cognitive impairment or dementia, and use of physical restraints [11]. While UI is common in older adults, it is not a normal part of aging, and routine screening and non-surgical treatment for UI have the potential to decrease morbidity and improve quality of life [11, 12].

2. The Current Climate of Screening

2.1 Patient and Primary Care Provider Comfort in Initiating Conversation

Despite the high prevalence of UI, and its significant negative impact on quality of life and well-being [13], UI is infrequently addressed at preventive healthcare visits and only 25-61% of women with UI seek care [14-18]. While patients prefer that clinicians initiate a discussion about UI [19],

clinicians are unlikely to bring it up. In one study of 900 women with UI, only 3% reported their provider initiated a discussion about UI [17]. In one survey of over 100 primary care providers (PCPs), most clinicians perceived UI to be an important topic, however, 72% reported screening only some patients or none at all [20]. The two most common barriers to screening for UI identified by PCPs were competing health priorities (83%) and assuming patients with bothersome UI would ask about treatment options (44%).

2.2 Current Recommendations and Quality Measures

Current UI screening guidelines for women from the Women's Preventive Services Initiative recommend screening all women 18 years and older for UI annually [21]. Screening women aged 65 years and older for UI is a Merit-based Incentive Payment System (MIPS) clinical quality measure (#048) by the Centers for Medicare and Medicaid Services, on the assumption that patients may not disclose incontinence symptoms and should be asked about them by a provider [21-24]. Furthermore, the Medicare Health Outcomes Survey (HOS) asks women about the impact of UI on their lives and whether their provider discussed and treated their UI. Patient survey responses are then aggregated and reported in the Healthcare Effectiveness Data and Information Set (HEDIS), a set of standardized performance measurements assessing the quality of care and service, as one of the few measures to be solely based on patient survey data [25-27]. The most recent results reported from 2017 indicate that 59% of individuals participating in both Medicare Health Maintenance Organization (HMO) and Preferred Provider Organization (PPO) endorsed discussing UI, while only 44% and 46% of individuals who reported having UI in HMO and PPO, respectively, endorsed discussing UI treatment options [25].

2.3 Evaluation of UI

Similar to depression, there are numerous validated incontinence questionnaires available. We recommend the '3 Incontinence Questionnaire' (Box 1), which asks about urine leakage and elucidates whether symptoms are associated with stress, urgency, or unspecified incontinence [28]. While these questionnaires exist, it is not necessary to determine UI type upon initial diagnosis since first-line treatment for all UI types is the same. Therefore, it is reasonable to inquire about urine leakage using plain language during a standard review of systems. We recommend PCPs screen for UI at annual preventive visits using the phrase, "During the last 3 months, have you leaked urine, even a small amount?" A positive response should prompt a urinalysis as outlined in Figure 1, which illustrates an algorithm for PCPs to screen, diagnose, and treat UI in female patients. As depicted in the algorithm, during the follow-up appointment in 2 months, if first-line treatments have failed, PCPs can determine UI type by asking patients if they experience urine leakage (1) "When you were performing some physical activity, such as coughing, sneezing, lifting, or exercising?", (2) "When you had the urge or the feeling that you needed to empty your bladder, but you couldn't get to the toilet fast enough?", and (3) "Without physical activity and without a sense of urgency," with a positive response indicating SUI, UUI, and unspecified incontinence, respectively. Appropriate International Classification of Disease Version 10 codes are listed below each of these diagnoses in Figure 1.

Box 1 3 Incontinence Questionnaire.

1. **During the last three months have you leaked urine (even a small amount)?**
    a. **Yes → Continue to question 2**
    b. **No → end of questions (no UI)**
2. **During the last three months did you leak urine? (check all that apply)**
    a. **When you were performing some physical activity, such as coughing, sneezing, lifting, or exercise?**
    b. **When you had the urge or the feeling that you needed to empty your bladder, but you couldn't get to the toilet fast enough?**
    c. **Without physical activity and without a sense of urgency?**
3. **During the last three months did you leak urine most often (check only one):**
    a. **When you were performing some physical activity, such as coughing, sneezing, lifting, or exercising? → SUI**
    b. **When you had the urge or the feeling that you needed to empty your bladder, but you couldn't get to the toilet fast enough? → UUI**
    c. **Without physical activity and without a sense of urgency? → Unspecified**

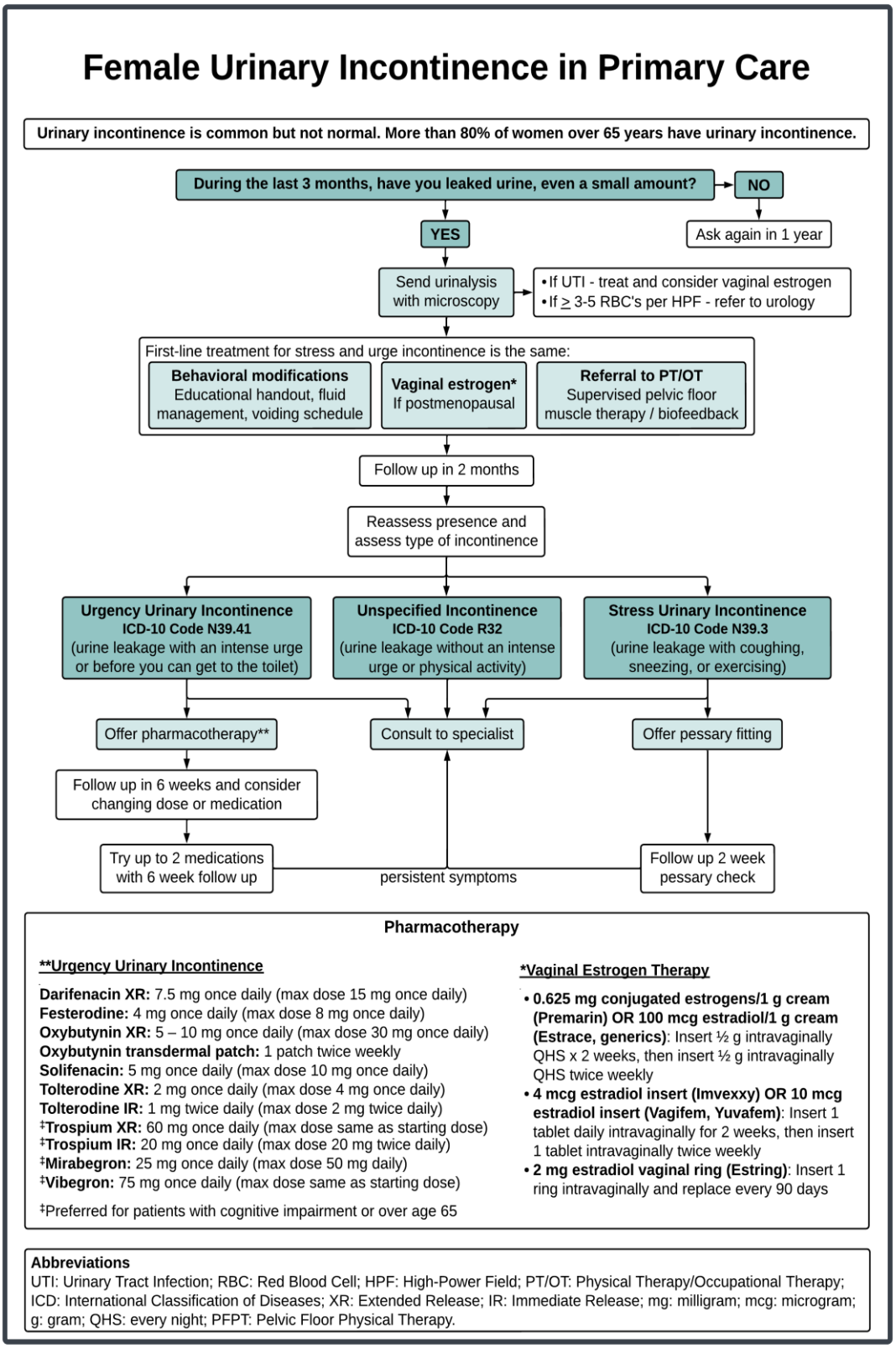

Figure 1 Female Urinary Incontinence in Primary Care Algorithm.

Generally, UI management should be triaged by UI type and patient goals of care. During the follow-up period, if first- and second-line treatments have failed for patients experiencing UI, PCPs can proceed with referrals to urology or urogynecology.

It is important to keep in mind that common comorbid conditions and medications can contribute to or exacerbate UI [29-32]. There is a higher prevalence of stroke, diabetes, high cholesterol, hypertension, arthritis, asthma, obesity, and depression among women with UI compared to those without [29, 30]. Studies evaluating medications associated with UI show conflicting data. In one study, multivariate logistic regression models were not robust for aspirin, opiates, atypical antipsychotics, tricyclic antidepressants, benzodiazepines, serotonin modulator antidepressants, corticosteroids, and proton pump inhibitors. However, there were significant associations with UI for antihistamines (OR 1.75; 95% CI 1.09-2.80), beta receptor agonists (OR 1.73; 95% CI 1.19-2.53), angiotensin II receptor blockers (OR 2.07; 95% CI 1.10-3.90), and systemic estrogens (OR 1.90; 95% CI 1.20-3.01) [29]. Another study demonstrated significant associations with UI for tranquilizers (OR 1.65; 95% CI 1.06-2.57), antidepressants (OR 1.75; 95% CI 1.04-2.94), hypnotics (OR 1.52; 95% CI 1.07-2.16), laxatives (OR 1.67; 95% CI 1.18-2.37), and antibiotics (OR 1.64; 95% CI 1.25-2.16). The same study did not demonstrate associations between UI and pain medications, narcotics, anti-hypertensives, and diuretics [30]. In our clinical experience, unless a patient has an onset of UI symptoms coinciding with medication addition or alteration, it is rare that medication management, other than that involving diuretics, resolves UI symptoms.

A UI-focused physical examination may be indicated based on symptoms and symptom severity [31, 32]. Evaluation of mental status, physical dexterity, and mobility can identify functional factors contributing to symptoms. An abdominal exam should be performed to evaluate for bladder distension or abdominopelvic mass, and tenderness in the suprapubic or flank regions, which may indicate lower or upper urinary tract infection. Inspection of the external genitalia (vulva, urethra, and perineum) may identify skin irritation from urine or protective undergarments and signs of estrogen deprivation (vulvovaginal atrophy, urethral caruncle). Asking the patient to Valsalva while in dorsal lithotomy detects pelvic organ prolapse (protrusion of vaginal tissue or cervix beyond the hymen). Finally, pelvic floor resting tone and muscle strength can be assessed by placing one lubricated finger gently in the vaginal canal and palpating the muscles at rest and then asking the patient to squeeze (to try to pull the examiner's finger inward and upward) [22, 31, 32]. If the pelvic floor muscles are firm or tender to palpation, or if instructions to squeeze result in minimal muscle contraction or paradoxical Valsalva, the patient may benefit from referral to physical or occupational therapy for pelvic floor muscle training. If the patient is able to contract her pelvic floor muscles without pain on exam, recommending a home exercise program to the patient is reasonable. Both the American Urogynecologic Society (www.augs.org) and the International Urogynecological Association (www.iuga.org) have educational leaflets that can be downloaded and provided to patients for free.

The only laboratory assessment routinely indicated to evaluate UI is a urinalysis with an office urine dipstick or a urinalysis with microscopy to assess for infection, hematuria, and glycosuria. Some guidelines also recommend assessment of post-void residual for patients with incontinence or other lower urinary tract symptoms. If there is suspicion of urinary retention (based on history of neuromuscular disease or exam findings of bladder distension, for example), an assessment of post-void residual (PVR) urine volume should be completed (with either a bladder scanner or straight catheterization). A value less than 150 mL suggests a normal PVR [13, 22, 31, 32] and is reassuring, but a number higher than 150 mL is not necessarily clinically relevant. We suggest considering referral to a specialist (urologist or urogynecologist) for urinary retention that may contribute to incontinence. The presence of microscopic hematuria, defined as more than 2 red blood cells per

high-powered field on microscopy, or elevated PVR, should prompt referral to urology or urogynecology for additional evaluation, which may include upper tract imaging, cystoscopy, and multichannel urodynamic testing. Urodynamic testing is not indicated prior to initiating therapy but may be used by subspecialists to guide advanced therapies.

3. Treatment Options

Similar to their screening and follow-up Medicare measures for UI, the Centers for Medicare and Medicaid Services also has a MIPS clinical quality measure (#050) regarding a documented care plan if a diagnosis of UI is utilized [33]. The Agency for Healthcare Research and Quality (AHRQ) and the Patient-Centered Outcomes Research Institute (PCORI) published a joint systematic review in 2018 that summarized the evidence-based nonsurgical treatments that can improve, and sometimes cure, UI symptoms in older adult women [34].

Regardless of UI type, first-line management of UI in women includes education, behavioral modifications, vaginal estrogen, pelvic floor muscle training, weight management, fluid management, avoiding bladder irritants, and other lifestyle modifications. Additional treatments may include oral medications, anti-incontinence devices, neuromodulation, and surgery [13, 22, 31, 32, 35-37].

Providers should follow up with patients in 2 months from treatment initiation to evaluate symptom improvement [32]. The management of incontinence should be directed by UI type and severity, associated level of bother, and patient goals of care [13, 31]. If first-line treatment has failed for patients experiencing SUI, patients may benefit from a pessary fitting [38]. There are several pessary shapes and sizes specific to SUI, so fitting should be performed by a trained provider. For patients experiencing UUI in which first-line treatments were not effective, PCPs can offer a pharmacotherapy medication (Table 1) and have the patient follow up again in 6 weeks as outlined in Figure 1. An appropriate medication should be identified for each patient based on their history. If first-line treatment fails for patients experiencing unspecified incontinence or second-line treatment fails for patients experiencing SUI or UUI, patients should be referred to urology or urogynecology.

Table 1 Medications for Management of Urgency Urinary Incontinence.

Medication	Starting Dose	Maximum Dose
Darifenacin XR (Enablex)	7.5 mg once daily	15 mg once daily
Festerodine (Toviaz)	4 mg once daily	8 mg once daily
Oxybutynin XR (Ditropan XL)	5-10 mg once daily	30 mg once daily
Oxybutynin IR (Ditropan)	5 mg two or three times daily	5 mg four times daily
Oxybutynin transdermal patch (Oxytrol)	1 patch once every 3-4 days	Same as starting dose
Tolterodine XR (Detrol LA)	2 mg once daily	4 mg once daily
Tolterodine IR (Detrol)	1 mg twice daily	2 mg twice daily
Solifenacin (Vesicare)	5 mg once daily	10 mg once daily
Trospium XR (Sanctura XR)	60 mg once daily	Same as starting dose
Trospium IR (Sanctura)	20 mg once daily	20 mg twice daily
Mirabegron (Myrbetriq)	25 mg once daily	50 mg daily
Vibegron (Gemtesa)	75 mg once daily	Same as starting dose

Early referral to urology or urogynecology should be considered for patients with a history of prior pelvic radiation or surgery, hematuria, urinary leakage without sensory awareness, recurrent urinary tract infections (2 or more culture-confirmed symptomatic infections in a 6 month period or 3 or more in 12 months), urinary retention, significant pelvic organ prolapse, or suspected fistula [22, 32].

3.1 Initial Treatment for UI

Women with UI should be counseled that conservative options improve symptoms for most patients [22, 31, 32, 39]. Initial therapy for UI may include education about fluid management, bladder training, the impact of weight and constipation on UI symptoms, pelvic floor muscle strengthening, and vaginal estrogen for postmenopausal women [22, 31, 32].

3.1.1 Education

There are several online resources for patient education through the American Urogynecologic Society (AUGS) (www.voicesforpfd.org) and the International Urogynecological Association (IUGA) (www.yourpelvicfloor.org). AUGS has printable patient information fact sheets in both English and Spanish (https://www.voicesforpfd.org/resources/fact-sheets-and-downloads/), including large print options, and IUGA has patient information leaflets in multiple languages (https://www.yourpelvicfloor.org/leaflets/) [22]. We recommend the AUGS handouts titled "Lifestyle and Behavioral Changes" (https://www.voicesforpfd.org/assets/2/6/LIFESTYLE_CHANGES.pdf) and "Pelvic Floor Muscle Exercises and Bladder Training" (https://www.voicesforpfd.org/assets/2/6/Bladder_Training.pdf), in addition to the IUGA handouts titled "Non-surgical Approaches to Managing Bladder Problems" (https://www.yourpelvicfloor.org/media/Non-Surgical_Approaches_to_Managing_Bladder_Problems_V1.pdf) and "Bladder Training" (https://www.yourpelvicfloor.org/media/Bladder_Training_RV2.pdf).

3.1.2 Behavioral Modifications

Fluid management can improve UI symptoms. Patients may be instructed that their goal fluid intake should be the number of ounces of their weight in kilograms, so a 70 kg woman may be advised to drink about 70 ounces of fluid daily (including all fluids, not just water). The Institute of Medicine recommends women over 65 should drink 91 ounces daily but this is likely excessive for patients with incontinence [40]. Adjusting fluid intake can reduce urinary frequency, urinary urgency, UI, and constipation [13, 22, 31]. Importantly, fluid restricting can worsen constipation, so patients should be counseled about the importance of adequate fluid intake as well as avoiding excessive fluid intake. Avoiding or reducing potential bladder irritants such as caffeine, carbonated beverages, alcohol, and artificial sweeteners may also reduce urinary urgency and UI symptoms [22, 31, 32]. A normal number of voids per day is 6-8, corresponding to a voiding interval of 3-4 hours. In women who report that they forget to void or do not experience a sensation to void until they have urgency, setting an alarm to remind them to void every 3 hours can be helpful. In women who void too frequently, gradually spacing the time between voids can allow the bladder to adapt to

holding more urine. Urge suppression and mental diversion techniques are helpful strategies for these behavioral modifications [22, 31].

3.1.3 Pelvic Floor Muscle Exercises

Pelvic floor muscle training improves UI and can be done with or without a referral to a nurse, physical therapist, or occupational therapist with pelvic floor expertise. There are various at-home pelvic health systems that utilize intravaginal devices to strengthen the pelvic floor. If high pelvic floor muscle tone or inability to contract the pelvic floor muscles is detected on physical exam, patients should be referred for supervised pelvic floor muscle training. Supervised pelvic floor muscle training allows for the assessment and conditioning of larger muscle groups that contribute to pelvic floor muscle function as well as adjunct biofeedback, which provides visual cues to help patients learn to contract, relax, and coordinate muscles [22, 31, 32, 36, 41].

3.1.4 Weight Management

Among patients who are overweight or obese, even modest weight loss is associated with improvements in UI symptoms. In one weight loss intervention study, women in the intervention group had a mean weight loss of 8.0% (7.8 kg) and at 6 months, the mean weekly number of incontinence episodes decreased by 47% in the intervention group, as compared to the control group with a mean weight loss of 1.6% (1.5 kg) and mean weekly number of incontinence episodes that decreased by 28% ($p = 0.01$) [31, 35].

3.1.5 Vaginal Estrogen Therapy

Estrogen deprivation coupled with aging can weaken the pelvic floor muscles, ligaments and tissues, which can lead to decreased support of the urethra [42]. There are estrogen receptors in the vagina, urethra, and bladder. During menopause and beyond, estrogen deprivation leads to decreased blood flow to these tissues, which may manifest as symptoms of vaginal dryness, urinary urgency, and incontinence. Local vaginal estrogen therapy does not have the same risks as systemic hormone therapy and should be considered for patients with these symptoms (Figure 1) [32]. Formulations include cream or tablet for which the recommended dose can be placed nightly for two weeks followed by twice weekly maintenance dosing, or a vaginal ring formulation that is removed and replaced with a new ring every 90 days [43].

3.1.6 Functional Urinary Incontinence

The physical or cognitive conditions that prevent a person from accessing the toilet are vast, and as such, the best strategies are individualized and aimed at optimizing the environment. Such strategies include: timed voiding every 2-3 hours, toileting aids, wearing easy-to-remove clothing, removing pathway clutter, ensuring good lighting, providing assistance or mobility aids, monitoring for cues to use the toilet (e.g., pulling at clothing or restlessness), or providing a bedside commode, especially during sleeping hours [2, 22].

3.1.7 Incontinence Care Products

Patients who use incontinence supplies to contain their urine leakage may be eligible to receive coverage by their insurance for products or may be able to use their Health Savings Account (HSA) or Flexible Spending Account (FSA) [8, 44]. Generally, individuals insured by Medicaid are eligible to receive coverage for their incontinence supplies, if the supplies are deemed medically necessary, while the majority of individuals who are insured by Medicare or private insurance companies do not receive coverage [45, 46]. However, even if an individual's insurance company does not provide coverage for incontinence products, patients may still be able to utilize their HSA or FSA [8]. Due to the high cost of incontinence products, informing patients about how they may be able to receive coverage can alleviate part of the cost-burden incontinence has on patients.

3.2 Additional Treatment for Urgency Urinary Incontinence

3.2.1 Oral Medications

If conservative management is not satisfactory for UUI symptom management, then women should be offered a trial of medication to improve symptoms (Table 1) [22]. The combination of behavioral therapy and medication is superior to medication alone for improvement in and cure of UUI [42]. While medications for UUI modestly decrease incontinence episodes by 30-60% per day (0.3-1.2 episodes), they should be used with caution in older adults [22, 47]. Anticholinergic medications competitively inhibit acetylcholine at postganglionic muscarinic receptors, resulting in smooth muscle relaxation in the bladder (and other organs) [48]. Common side effects include dry eyes, dry mouth, constipation, urinary retention, dizziness, and blurry vision [22, 31, 49]. Long-term cumulative anticholinergic use is correlated with an increased risk of all-cause dementia and Alzheimer's disease, and prescribers should be comfortable counseling about these side effects [22, 31].

Beta 3 adrenergic agonists, like Mirabegron or Vibegron, act by promoting bladder muscle relaxation and are presumed to be safer in patients at risk for or with existing cognitive impairment. Side effects of beta-adrenergic agonists can include hypertension, urinary tract infection, nasopharyngitis, urinary retention, and constipation, which are often mild [50]. Mirabegron has been associated with a mild increase in blood pressure and blood pressure should be monitored while using this medication; Vibegron does not have this association. Mirabegron use is contraindicated in patients with uncontrolled hypertension.

If a patient reports symptoms of incomplete bladder emptying or has symptoms that appear to be worsening rather than improving, post-void residual should be assessed using catheterization or an ultrasound bladder scanner to exclude urinary retention [22, 31]. If a patient does not experience bothersome side effects and has inadequate subjective or objective improvement in symptoms, the dose should be increased until the maximum dose is achieved. If patients do not achieve significant improvement in symptoms after 12 weeks of the maximum dose of the medication, it should be discontinued [22].

3.2.2 Advanced Therapies for Urgency Urinary Incontinence

If UUI symptoms are not controlled to patients' satisfaction with medications, then women can be referred to urology (https://www.urologyhealth.org/find-a-urologist/) or urogynecology (https://www.voicesforpfd.org/find-a-provider/) specialists, who may offer advanced therapies such as percutaneous tibial nerve stimulation, intradetrusor injection of onabotulinum toxin A, or sacral neuromodulation [22, 31, 32].

3.3 Additional Treatment for Stress Urinary Incontinence

If conservative management is not satisfactory for SUI symptom management, then women can be referred to urology or urogynecology specialists for counseling about anti-incontinence devices, such as pessaries, or for anti-incontinence surgical procedures [22].

3.3.1 Intravaginal Devices

An incontinence pessary is a medical-grade silicone-based intravaginal device that supports the anterior vaginal wall and bladder neck. There are several shapes and sizes specific to SUI, so fitting is performed by a trained provider, and a reusable device is dispensed to the patient following successful fitting. Pessaries may be inserted and removed by the patient independently or may be left in place and managed with assistance from a healthcare provider every 3-6 months. Common side effects include vaginal discharge, spotting, or breaches in the vaginal epithelium, for which treatment with vaginal estrogen is often initiated. Though rare, pessaries left in place for extended periods of time have been associated with fistula development, so it is important to confirm that a patient using a pessary has a management plan with the fitting provider [51, 52].

Whereas incontinence pessaries have been studied extensively, there are newer intravaginal devices that are marketed directly to consumers, and patients may also try these products. Like incontinence pessaries, the goal of these intravaginal devices is to provide support under the bladder neck and urethra [53]. Examples of direct-to-consumer options are disposable intravaginal devices that help prevent bladder leaks, such as Poise Impressa or Revive [54, 55]. Uresta is a reusable intravaginal device for patients to self-manage their symptoms. Uresta can be prescribed by a healthcare provider without the need to do in-office fittings and can then be dispensed to the patient directly via HealthWarehouse.com (https://www.healthwarehouse.com) [56].

3.3.2 Surgical and Office-Based Procedures

Procedures to treat SUI are broadly categorized into slings and urethral bulking procedures. Urethral bulking procedures are less effective but also have lower associated risks. Thus, they are an excellent option for medically frail patients with bothersome SUI. Slings may utilize synthetic or biological material. Mid-urethral slings utilizing permanent mesh are the best-studied incontinence surgeries in history and studies of these procedures consistently show high levels of success and patient satisfaction. These mesh-based mid-urethral sling procedures are approved by the US Food and Drug Administration (FDA) and have very low rates of mesh complications [57].

4. Conclusion

With increasing pressures and time constraints facing primary care providers, it is daunting to consider adding yet another condition for which to screen to the list. In recognition of this challenge, in 2022 AHRQ awarded $15 million to 5 research sites across the US to generate evidence about how to best support primary care practices to implement screening and treatment for urinary incontinence in adult women through a mechanism called EvidenceNOW: Managing Urinary Incontinence [58]. Later in 2022, PCORI awarded $2.5 million to support the dissemination and implementation of nonsurgical management of UI in women 60 years and over [59, 60], underscoring recognition by multiple federal agencies that UI is an increasing health threat as our population ages.

The prevalence of UI in US women 65 years and older is greater than 80%, corresponding to more than 24 million US women. Despite this high prevalence and associated negative impact on quality of life and well-being, UI is infrequently addressed. Considering the immense burden of this disease, the evaluation and initial management of UI is not only within the scope of practice of PCPs, but is imperative.

Author Contributions

Dr. UP and Ms. MM wrote the draft of the manuscript. Dr. JN and Dr. HB were responsible for final editing of the manuscript.

Competing Interests

HB receives royalties from Wolters-Kluwer, Inc and Springer, Inc for publications she has authored. HB is a consultant for Grand Rounds, Inc. The other authors have no disclosures.

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