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Urinary incontinence in women - the overview of pharmacological and surgical methods

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Abstract

Introduction and purpose of the work:

Urinary incontinence (UI) is a common problem among women and the incidence increases with age. It is estimated that about 50% of women will be affected by this problem. There are 5 types of urinary incontinence: exercise, pressure, mixed, overflow and functional. Stress UI is the most common cause among young women, while stress UI is the second most common cause among older women. The widespread use of this phenomenon makes it a significant economic burden.

State of knowledge (brief description):

Due to the different types of UI and its many causes, treating this disorder becomes a significant challenge. It is important to use combination therapy, starting with pelvic floor muscle strengthening exercise, lifestyle modification, weight loss, and smoking cessation, followed by drug therapy and surgery as necessary.

Summary:

Currently, many drugs are used in the treatment of urinary incontinence, with different mechanisms of action, which allow the treatment of various types of UI, but pharmacotherapy often does not bring the expected benefits. Surgical treatment appears to be a promising form of treatment, but more research is needed on the long-term effects.

Key words: urinary incontinence, treatment, women, pharmacology, surgery

Introduction

Urinary incontinence (UI) is a common problem of women around the world leading to a reduction in the quality of life and is defined as any complaint of involuntary urination. As its occurrence is positively correlated with age, it is estimated that approximately 50% of women will experience some form of urinary incontinence in their lifetime. UI represents a significant economic burden with annual costs of \$ 19.5-76 billion per year. [1]

Urinary incontinence can be classified as transient or chronic. Transient UI is the leakage of urine that resolves when the cause is removed. The chronic form does not go away on its own and five subtypes can be distinguished: exercise, pressure, mixed, overflow and functional. Stress UI is the most common cause of urinary incontinence in younger women and the second most common cause in older women. This is due to a weakening of the sphincter. Urge UI is caused by detrusor overactivity. In the mixed form of UI, stress urinary incontinence and urge incontinence coexist and its incidence increases with age. Overflow UI is caused by excessive bladder filling caused by impaired detrusor contractility and / or obstruction of the bladder outlet. Functional UI is caused by functional, cognitive, or motor difficulties that result in the patient having an impaired ability to use the toilet, but without impaired bladder function or neurological control of urination. [2]

In a meta-analysis conducted by John et al., Aimed at assessing the relationship between urinary incontinence and increased mortality, it showed that UI is a predictor of higher mortality, especially in the geriatric population. [3]

Urinary incontinence is a pathological condition that significantly reduces the quality of life. Patients with UI suffer from depression much more often, their social functions become limited, and their sexual life also deteriorates. [4]

Treatment of urinary incontinence depends on the type and cause as well as the severity of the symptoms. If possible, it is recommended to eliminate the cause first. Regardless of the type of urinary incontinence, beneficial effects are achieved by lifestyle changes, weight reduction in overweight or obese patients, reduction or termination of caffeine and alcohol consumption, and reduction of excessive fluid intake. Beneficial effects are also obtained by regular training of the pelvic floor muscles under the supervision of a qualified person with adequate experience. [1], [5]

Treatment of urinary incontinence in women includes pharmacotherapy and surgery. The following overview aims to compare the treatments currently available.

Pharmacological methods

Pharmacological agents are the next step when lifestyle changes, behavioral and physical therapy are ineffective in treating urinary incontinence in women. The selection of appropriate pharmacological agents depends on the cause of urinary incontinence and comorbidities.[5] Moreover, the treatment of urinary incontinence focuses mainly on improving the quality of life, therefore the selection of appropriate pharmacotherapy should be based on the patient's preferences. [6]

Antimuscarinics

Acetylcholine (Ach) is released from cholinergic nerve endings, which stimulates muscarinic receptors and mediates voiding contraction in humans. [7] There are five types of muscarinic receptors (M1-M5), while the types M2 and M3 have been detected in the human bladder. [8] There are:

Non-selective antimuscarinic

- Fesoterodine
- Oxybutynin
- Propiverine
- Tolterodine
- Trospium

Selective M3 antimuscarinic

- Darifenacin
- Imidafenacin
- Solifenacin

Antimuscarinic drugs are mainly used in the pharmacotherapy of overactive bladder (OAB) and urgency incontinence, they lead to a reduction in the frequency of urination and, to a lesser extent, nocturia. [9], [10] Despite the proven therapeutic effectiveness of antimuscarinic drugs, their use may lead to side effects, including dry mouth, drowsiness, constipation and blurred vision, which may affect persistence with long-term treatment and compliance with treatment. [9] Moreover, dry cavity was the main reason for treatment discontinuation. [11] The highest rate of dry mouth occurred with the use of oxybutynin. [12], [13]

In recent years, research has been carried out on antimuscarinic molecules to reduce the number of side effects and increase the affinity for M3.

Indafenacin is a new antimuscarinic drug with higher affinity for M1 and M3 receptors and lower affinity for M2. Compared to other drugs, imidafenacin showed similar efficacy, but caused fewer episodes of nocturia, dry mouth and constipation, therefore it is preferred in long-term therapy. [14]

Beta-3-Agonists

The beta-3 adrenergic receptor is the most common subtype of beta-adrenergic receptors in the bladder, where it participates in detrusor relaxation through adrenaline. [15] Mirabegron is the representative of this group of drugs used in the treatment of urinary incontinence. Studies have shown similar efficacy compared to available antimuscarinic drugs, while dry

mouth was less common in mirabegron. [16] A multicenter prospective study comparing mirabegron with antimuscarinic therapy (FAVOR) showed a significant improvement in satisfaction rates with mirabegron treatment of urinary incontinence in patients previously treated with antimuscarinic drugs. [17], [18] Side effects occurring during treatment with mirabegron include: nasopharyngitis, arterial hypertension and urinary tract infection. [19] Treatment with mirabegron was maintained much longer than with antimuscarinic drugs when administered as first or second line therapy. [20]

Vibegron is a new, potent and selective agonist of beta-3-adrenergic receptors, which will significantly reduce micturition, incontinence and urgency episodes, and increase the volume of urine output. [21], [22] This drug has not shown an increased incidence of hypertension compared to placebo. [23] Virabegron showed greater efficacy in reducing total incontinence episodes and urine volume compared to mirabegron. [24]

Solabegron is a highly selective beta-3 adrenoceptor agonist. Solabegron, compared with placebo, statistically reduces the number of incontinence episodes and increases the volume of urine output. Solabegron had no effect on heart rate and blood pressure. [25]

Phosphodiesterase-5 Inhibitors

Phosphodiesterase 5 (PDE5i) inhibitors, by inhibiting the degradation of guanosine monophosphate (cGMP), prolong the physiological effects of nitric oxide (NO), which affects the smooth muscle tone. [26] Recent studies in rats show that tadalafil has the effect of ameliorating bladder hyperreactivity by increasing urinary NO levels and detrusor cGMP levels. [27] Another study found that tadalafil (5 mg / d) reduced the number of incontinence and urgency episodes compared to placebo. Moreover, in the case of the dose of 5 mg / day, no serious side effects were found. [28]

Serotonin-noradrenaline reuptake inhibitors

Duloxetine is a serotonin norepinephrine reuptake inhibitor (SNRI) that increases the levels of these neurotransmitters in the presympathetic neuron, which is located in the Onuf nucleus of the spinal cord. The action of SNRI and the Onuf nucleus leads to an increase in the activity of the urethral sphincter and an increase in urethral pressure. [29] In the European Union, duloxetine has been approved for the treatment of stress urinary incontinence after initial studies suggesting its effectiveness, while in the United States, due to concerns about side effects such as suicidal ideation, the drug has not been approved. [30] Duloxetine is not indicated as the first-line treatment, its efficacy in urinary incontinence treatment is weak, therefore it is not widely used. [31]

Surgical methods for the treatment of urinary incontinence

When conservative management is exhausted and has failed, surgical treatment is possible. The choice of treatment should be adapted to the type of UI and the severity of symptoms. Surgical treatment of stress UI is mainly aimed at increasing the support of the urethra and urethral sphincter. On the other hand, in the treatment of urge, UI is primarily aimed at

neuromodulation of the sacral segment. Studies have shown that the people who benefit most from surgery are patients with hypermobility of the urethra. [1]

Sacral neuromodulation (SNM)

Sacral neuromodulation (SNM) was developed by Tanagho and Schmidt in 1982. They showed that continuous stimulation of the S3 sacral nerve root using an electrode connected to an implantable pulse generator can influence detrusor and sphincter activity and regulate micturition reflexes. SNM is a potential treatment for patients with various forms of bladder dysfunction. [32]

The exact mechanism by which SNM works is not fully understood. The SNM is believed to block the activity of the C fibers, which become more active due to inflammation or neurological disorders and can activate the emptying reflex when the bladder is full. The blockage of the C fibers thus leads to the inhibition of irregular urination. In addition, it seems that SNM leads to the relaxation of the muscles of the fundus of the uterus and urethra, which facilitates the initiation of the voiding process in patients with impaired pressure in the bladder and its incomplete emptying. Moreover, for urgency and frequency of urination, it is suggested that SNM blocks or otherwise interferes with the afferent input to the sacral spinal cord, which inhibits detrusor overactivity. [33]

SNM is a method recommended for treatment-resistant urinary tract dysfunctions, including: urge UI, urinary retention, and urgency. [34]

Contraindications to surgical treatment with the use of SNM include urinary tract obstruction, current infection in the pelvic organs, and severe or rapidly progressing neurological disease. Age and comorbidities are not a contraindication, however, there are reports that in patients over 55 years of age with 3 or more comorbid chronic diseases, the effects of treatment are weaker. The most common side effect is loss of treatment effectiveness. [33]

A study by McCrery et al. Showed that after 6 months, 90% of participants experienced a clinically and statistically significant improvement after SNM. [35]

In a meta-analysis of 9 studies comparing the effects of onabotulinumoxin A and SNM in treatment-resistant urinary incontinence, SNM was shown to be worse in terms of efficacy, but better in terms of safety. [36]

Another meta-analysis showed that in 8 out of 17 studies, in women with pelvic floor disorders, especially bladder dysfunction, SNM has a positive effect on sexual function ($p = 0.0001$). [37]

Traditional sling operations

Traditional sling operations are used in the treatment of stress urinary incontinence in women. The procedure is based on supporting the bladder with a strip of material, synthetic (Teflon, Mersilene tape in a silicon tube, Lyodura, polytetrafluoroethylene, Marlex mesh, silastic), biological autologous (rectus fascia, fascia lata, pubococcygeal muscle, vaginal wall, aponeurosis, pyramidalis fascia) or biological exogenous (ox fascia, porcine dermis). The purpose of surgery is to strengthen or restore support to the woman's urethra when making sudden movements, such as coughing. Traditional suburethral sling operation requires

abdominal and vaginal connection. The strips of material are tunneled under the urethra and attached to the rectus muscle or iliopectineal ligaments. Compared to minimally invasive slings, traditional sling operations appear to be just as effective, but have a higher rate of adverse effects. However, due to the short follow-up period and variable quality of the evidence, this should be interpreted with caution. [38]

Mid-urethral Sling (MUS)

Currently, the most commonly used treatments for stress urinary incontinence are the use of a synthetic mid-urethral sling (MUS) with a cure rate > 80%. There are three main routes of sling insertion: the retropubic route, the transobturator route, and using "single incision" or "mini-sling." The essence of this treatment is the placement of a tension-free polypropylene tape to support the urethra from the vaginal side. The synthetic mesh is placed inside the vagina at the level of the mid-urethra and is passed retropubically or via the transobturator approach. No sutures are used in any of these tension-free procedures. The mesh is held in place by body tissues and fibrosis. [5]

In the Tension-free Vaginal Tape (TVT) method, the sling is inserted through a small incision made in the vagina below the urethra. The two ends of the sling are drawn on either side of the urethra, forming a loose loop around it. The ends extend outward through two small incisions located above the pubic bone. A study by Nilsson et al. Demonstrated a subjective and objective cure rate of 77% and 90% at 11.5 years after TVT. [39], [40]

In the Transobturator Tape (TOT) method, a small incision is made in the vagina in the inguinal fold on the medial side and a sling is placed under the middle of the urethra and vagina. It goes through the obturator foramen. This technique enables the achievement of similar clinical effectiveness as the classic retropubic technique, with a significantly reduced number of intraoperative complications. [40]

In a study by Lee et al. Aimed at examining the effect of obesity on the effectiveness of TOT and the assessment of postoperative complications, it was shown that the TOT procedure is effective regardless of the patient's BMI, while obese women more often suffered from postoperative urinary complications. [41]

Mayekar et al. Conducted a study to assess the results and satisfaction of patients after TOT surgery. Successful surgical treatment with the TOT method was observed in all patients at the time of discharge from the hospital. After 5 years of follow-up, 2 out of 67 patients had UI recurrence, but they did not complain about symptoms. [42]

In the study by Sik et al. Two years of follow-up after TOT surgery, a significant improvement in the quality of life was found in the study participants compared to the preoperative period, and the objective cure rate was 88.5%. [43]

The mini-sling procedure is similar to the TVT or TOT procedure. The mini-sling method uses a shorter strip of mesh to support the urethra and may have a small, self-fastening anchor to hold it in place. This prevents additional skin incisions from being made. [40] Theoretically, the mini-sling procedure allows to avoid bladder perforation and large vessel damage that may occur during postoperative procedures, as well as postoperative thigh and groin pain that may occur after transobturator surgery. [40] Two randomized clinical trials

comparing TOT and mini-sling showed a shorter duration of pain and its intensity after surgery, while maintaining similar efficacy and safety. [44], [45]

The RCT conducted by Emami et al. Compared UI treatment with the TOT method and the mini-sling method. It has been shown that in patients treated with the mini-sling method, the duration of the procedure, intraoperative bleeding, hospitalization, pain and complications were significantly lower with similar efficacy. [46]

Tissue Fixation System (TFS)

The Tissue Fixation System is an innovative method of treating urinary incontinence, first described in 2005. This method uses two-polypropylene anchors to fix a macropore polypropylene mesh sling at the mid-urethra into the fascial structures behind the urogenital diaphragm, below the Space of Retzius. The treatment does not require perforation of the suprapubic skin or the perineum. In a study by Nakamura et al. A three-year treatment efficacy after TFS surgery was reported in 90% of patients. [47]

The study by Sekiguchi et al. Showed that the TFS method is simple, safe and effective. The cure rate after 12 months was 90.9%. [48]

Unlike meshes that block organ descent, TFS works by restoring ligament (pubourethral, cardinal, uterosacral, tendinous arch of pelvic fascia, perineal body) support and is also used to treat pelvic organ prolapse. In a study by Inoue et al. After 12 months, the recovery of prolapse was achieved by 90% of the examined patients. [49]

TVT-Secur

TVT-Secur (TVT-S) is a newer generation of tension-free suburethral slings introduced in 2005, aiming at even greater reduction of complications. The TVT-Secur technique requires one incision, uses a smaller total amount of mesh, and has no exit points for the mesh. [50]

In a study by Shin et al. On a group of 51 patients who underwent TVT-S procedure, the 2-year cure rate was 76%. Most of the patients reported a significant improvement in their quality of life. During the 2-year follow-up, no significant complications related to TVT-S were found. [51]

A multicentre, randomized, prospective study by Hamer et al. Comparing the effectiveness of TVT and TVT-S treatment showed that one year after surgery, both subjective and objective cure rates were significantly lower for the TVT-Secur procedure than for TVT (subjective cure: TVT 98%, TVT-Secur 80%, objective healing: TVT 94%, TVT-Secur 71%). [52]

In the study by Serdinsek et al., It was aimed at finding the reason for the lower effectiveness of the TVT-S method. An ultrasound examination was carried out in a randomized trial with a 3-year follow-up. The study showed a significantly higher percentage of positive exercise tests in the TVT-S groups compared to the TOT group. It is believed that the lower effectiveness of TVT-S may be caused by inadequate fixation and increasing tape descent. [53]

Intravesical onabotulinumtoxin A injections

Intravesical injection of OnabotulinumtoxinA is classified as a third line treatment for urinary incontinence. The mechanism of its action is based on the neuromodulation of the detrusor presynaptic neuromuscular junctions. The injections should be repeated in the event of recurrence of symptoms - every 9-12 months. The efficacy of OnabotulinumtoxinA is similar to that of oral drugs. A side effect of this method may be transient urinary retention with subsequent catheterization of patients and urinary tract infections. [5]

In a study by Yokoyama et al., Aimed at assessing the efficacy and safety of OnabotulinumtoxinA in patients with overactive bladder and urinary incontinence, it was shown that in the OnabotulinumtoxinA group, a significantly greater decrease in the mean number of daily urinary incontinence episodes was observed compared to placebo ($p < 0.001$). Adverse reactions occurring more frequently in the group taking onabotulinumtoxin A are urinary tract infection, painful urination, urinary retention and increased residual urine volume after urination. [54]

In a meta-analysis of RCTs, OnabotulinumtoxinA was shown to significantly reduce the number of urge incontinence episodes compared with placebo. Urinary tract infections occurred more frequently in patients treated with OnabotulinumtoxinA than in patients treated with placebo. [55]

Burch's Colposuspension

Burch's colposuspension is a method of surgical treatment of stress urinary incontinence, especially when it is caused by excessive mobility of the urethra. For a long time, this procedure was considered the gold standard in the treatment of SUI. The foundations of today's colposuspension technique were laid in 1958 by John C. Burch [56]

Open retropubic colposuspension elevates and fixes the tissues around the bladder neck and the proximal part of the urethra behind the front of the pubic bones to improve urethral closure. [57] Since the development of the Burch method, many modifications have been developed, such as Cowan and Morgan modification or Tanagho modification. [58], [59]

Burch's colposuspension is a highly effective surgical treatment of SUI with a low recurrence rate. For persistent or recurrent SUI after an unsuccessful MUS treatment attempt, Burch colposuspension is a second-line treatment option. [56]

In a meta-analysis of 55 trials involving a total of 5417 women during the first year, the overall cure rate is 85-90% and 70% after five years.[60]

A meta-analysis of 28 RTCs comparing the efficacy and safety of Burch's colposuspension, MUS and pubovaginal slings for urinary incontinence treatment showed that patients who underwent MUS had higher overall ($p = 0.003$) and objective ($p = 0.001$) cure rates than patients who underwent colposuspension surgery. [61]

Discussion

Urinary incontinence is a common problem for women all over the world and causes a significant economic burden and a reduction in quality of life. Inadequately treated UI can lead to depression, among other things, as well as systemic infections, skin diseases and injuries, and even hip fractures during falls, which occur when patients rush to the toilet. UI

may be unreported by patients for a number of reasons, including shame, the belief that it is a natural stage of aging, and a lack of knowledge of available treatments. This leads to a significant percentage of undiagnosed UI cases and no treatment. [62], [63]

The treatment of UI is gradual, depending on the subtype of urinary incontinence that occurs. Starting with conservative treatment, through the implementation of pharmacotherapy and finally surgical intervention. Pelvic floor muscle strengthening exercise, lifestyle modification, weight loss, and smoking cessation are the recommended treatment for all UI cases.

A meta-analysis of 94 RCTs to evaluate the efficacy of pharmacological treatment of urge UI showed that the use of drugs had little benefit. [64]

Newer minimal access surgical treatments appear to be promising compared to Burch open colposuspension. However, their long-term effectiveness is limited and must be closely monitored.

As we are dealing with a growing population of elderly people in society, it is reasonable to expect an even higher prevalence of urinary incontinence. UI in women, being such a common and curable condition, deserves more attention from all health care providers.

Summary

Urinary incontinence is a common condition of women. Treatment of UI should begin with conservative management, in case of failure, move on to invasive treatment, until the patient is cured or life improves. In addition to lifestyle modifications, pharmacological and surgical treatments are available. Drugs used to treat UI include: Antimuscarinics (e.g. tolterodine, solifenacin), Beta-3-Agonists (e.g. Mirabegron, Virabegron), Phosphodiesterase 5 inhibitors (tadalafil) and Serotonin-noradrenaline reuptake inhibitors (duloxetine). The surgical methods of UI treatment in women include: Sacral neuromodulation, Traditional sling operations, Mid-urethral Sling (MUS), Tissue Fixation System (TFS), TVT-Secur, Intravesical onabotulinumtoxin A injections, colposuspension. The key is to choose the best method for the patient that meets her needs.

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