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PHARMACOTHERAPIES AND DRUG DEVELOPMENT/AGENTS (ES ROVNER, SECTION EDITOR)

Pharmaceutical Options for Stress Urinary Incontinence

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Abstract

Purpose of Review We review the currently available pharmaceutical options for SUI.

Recent Findings Pharmaceutical options for SUI are either drugs that manipulate hormones or those that impact neurotransmitter levels. Local estrogen replenishment has been associated with improved OAB symptoms in postmenopausal women, but its impact on SUI is unclear. Subjective improvement may be noted, while objective outcome indices are typically unchanged. There is weak evidence to suggest that any adrenergic agonist is better than placebo in improving objective incontinence measures. Both alpha- and beta-adrenergic agonists are associated with significant side effects. Duloxetine, a serotonin and norepinephrine reuptake inhibitor (SNRI), has been shown to improve both objective and subjective outcome indices, but it is associated with significant side effects and is not FDA-approved. Evidence for the use of TAS-303, a norepinephrine reuptake inhibitor, is currently in the early stages and its clinically significant improvement and durability are unknown at this time. Finally, selective androgen receptor modulators (SARM) have shown promise in both animal and early human studies; however, a preliminary report from a large, multi-institutional, placebo-controlled trial of one of these agents (enobosarm reported that this drug did not achieve statistical significance in its primary endpoint compared to placebo. Overall, the drug was well tolerated.

Summary The majority of drugs available for SUI treatment are associated with limited improvement, unknown durability, and potential for significant side effects. There is some evidence for efficacy of both SNRIs and SARMs; however, more research is needed. At present, any use of medications for SUI is off-label in the USA.

Keywords Stress urinary incontinence · Estrogen · Duloxetine · Selective androgen receptor modulators

Introduction

Stress urinary incontinence (SUI) is defined by the International Continence Society (ICS) as "the complaint of any involuntary loss of urine on effort or physical exertion (e.g., sporting activities) or on sneezing or coughing" [1]. This type of incontinence has been traditionally attributed to a defect in fascial support of the urethra or bladder neck (urethral hypermobility), inadequate urethral coaptation (intrinsic sphincter deficiency), or a combination of the two. As such, treatment has been aimed at improving fascial tone with pelvic floor muscle training (PFMT) and biofeedback, surgically augmenting or buttressing weak fascial support with slings and bladder neck suspensions, and improving urethral coaptation with periurethral bulking or slings. All of these options are supported by the most recent AUA/SUFU Stress Urinary Incontinence Guidelines [2•].

While there is a lengthy history of pharmaceutical interventions for the treatment of urgency urinary incontinence (UUI), oral drug therapy are conspicuous by their absence in the SUI guidelines owing to the lack of durable outcomes and concerning adverse event profiles. With the relatively recent introduction of centrally active drugs, the role of pharmaceutical intervention for SUI merits reevaluation. We aim to review the currently available pharmaceutical options for SUI and discuss those medications that are in development, or already in use in other parts of the world.

This article is part of the Topical Collection on *Pharmacotherapies and Drug Development/Agents*

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Targets for Drug Treatment of SUI

Hormonal Manipulation

There is ample evidence supporting a relationship between hormones and urinary incontinence, albeit an inconsistent one. Epidemiological studies have shown that the drop in systemic estrogen levels brought on by menopause is associated with an increase in the prevalence of SUI [3, 4]. Perimenopausal and postmenopausal women with SUI may have significantly lower serum estradiol levels compared to age- and BMI-matched continent controls [5], and as many as 70% of incontinent post-menopausal women have related the onset of their incontinence to their final menstrual period [6]. On the other hand, some authors have reported that higher circulating estradiol levels may be associated with urinary incontinence [7], or there may be no association at all [8].

Since estrogen receptors can be found in urogenital organs and tissues involved in the continence mechanism (e.g., vagina, urethra, bladder, and pelvic floor musculature [9, 10]), it is intuitive to propose that local estrogen deficiency is a potential factor in the development of urinary incontinence. Indeed, the expression of estrogen receptors α and β in vaginal endothelia, smooth muscle cells, and fibrocytes may be significantly lower in pre-menopausal women with SUI compared with their stress-continent counterparts [11]. Chung and Bai showed that estrogen receptors might affect the pelvic support mechanism by playing a role in the synthesis and breakdown of collagen [12]. Furthermore, estrogens may increase urethral resistance by enhancing the amount of periurethral vasculature [13], while there may be an inverse correlation between serum estradiol levels and urethral hypermobility, a major mechanism underlying SUI [14]. Finally, estrogen may also increase the bladder sensory threshold, increase the number of epithelial cells lining the urethra and bladder, and increase the number and sensitivity of α-adrenergic receptors [15].

Manipulation of Central and Peripheral Neurotransmitters

There are several potential neurotransmitter targets in the continence mechanism. Two smooth muscle layers, a thick inner/longitudinal layer and a thinner middle/circular one, encircle the female urethra. An outer striated muscle layer (rhabdosphincter) surrounds the midurethra. Both smooth and striated muscles are tonically active during urinary storage, and rhabdosphincter activity increases with increases in intra-abdominal pressure. Menopause has been associated with atrophy of the rhabdosphincter and subsequent SUI [16].

Along its length, the urethra is lined by noradrenergic-mediated smooth muscle fibers, which contribute to resting urethral tone. Since the α1A adrenoceptor mediates contractile responses to norepinephrine in the urethra and bladder neck, an α1A-adrenoceptor agonist would, in theory, be expected to promote continence [17]. Contraction of the rhabdosphincter in response to increases in abdominal pressure is a result of noradrenergic and serotonergic signaling at the level of Onuf's nucleus in the ventral horn of the sacral spinal cord and subsequent pudendal nerve firing [18]. Hence, an increase in norepinephrine and serotonin signaling in these areas may increase urethral tone and contractility and theoretically improve symptoms of SUI.

Finally, β2- and β3-adrenergic receptors mediate relaxation of smooth muscle in the urethra and bladder, respectively [19]. While β3-adrenoceptor agonists have been proven to be effective treatments for overactive bladder, other drugs with action on β-adrenoceptors have not gained popularity for SUI. β-Adrenergic receptor antagonists are hypothesized to potentiate the activity of norepinephrine on α-adrenergic receptors and increase outlet resistance [15].

Clinical Outcomes of Estrogen for SUI

The use of estrogen-containing compounds has an impact on continence. In a review of over 12,000 women (57% premenopausal) from the National Health and Nutritional Examination Survey database, Cardenas-Trowers et al. cited varied associations between urinary incontinence (UI) and the type and route of hormone use [20]. In premenopausal women, the use of birth control pills, estrogen/progestin pills, and estrogen-only patches was significantly associated with UI, while the use of estrogen-only pills and estrogen/progestin pills was significantly associated with UI in postmenopausal women. Neither the estrogen patch nor the estrogen/progestin patch was associated with UI in postmenopausal women. In a review of several trial registries encompassing over 40,000 women, postmenopausal women using estrogen-only therapy and estrogen plus progestin had significantly higher risk of UI per 10,000 person-years, (1261 more cases [95% CI, 880 to 1689]) and [876 more cases [95% CI, 606 to 1168]), compared with placebo, respectively [21]. It must be noted that the definition of UI did not differentiate between UUI and SUI.

The Cochrane Review by Cody et al. identified 34 trials that encompassed nearly 20,000 women, with 17 trials recruiting women with SUI and five with mixed urinary incontinence (MUI) [22]. Roughly, half of the trials investigated systemic estrogen administration and the remainder evaluated local administration. The combined result of six trials of oral conjugated equine estrogens resulted in worse UI compared with placebo (RR 1.32, 95% CI 1.17 to 1.48) with the result heavily weighted by a subgroup of women from the trial by Hendrix et al., which had over 16,000 participants and 1-year follow-up [23]. There was some evidence that estrogens administered vaginally may improve UI (RR 0.74, 95% CI 0.64 to 0.86); however, the evidence was limited by small sample sizes and variations in the types, dosages, and durations of

estrogen treatment. The data regarding the impact of estrogen supplementation on SUI, specifically, was inconclusive as it was also based on relatively small trials with short follow-up periods.

On the other hand, a meta-analysis of 11 randomized controlled trials (RCTs) of estrogen therapy encompassing 430 women found that estrogen therapies were associated with statistically significant improvements in all outcome variables, including diurnal and nocturnal frequency, urgency, number of UI episodes, first sensation to void, and bladder capacity [24]. Local therapies had statistically significant beneficial effects on all outcome variables; however, systemic therapies were only associated with significant improvements in UI episodes and first sensation to void while nocturnal frequency actually worsened.

In a prospective study from three centers in South Africa, Australia, and the Netherlands, Weber et al. attempted to assess subjective and objective SUI symptoms before and after 6 weeks of topical estrogen therapy [25•]. Half of the 68 participants reported subjective improvement on the Patient Global Impression of Improvement scale, and a significant improvement on the Urogenital Distress Inventory stress domain was observed after treatment. However, baseline and repeat cough pad tests demonstrated a wide variation with no significant difference.

Finally, Balk et al. performed a network meta-analysis of 84 RCTs reporting cure or improvement outcomes for UI (32 in SUI, 16 in UUI, 4 in MUI, and 32 in any, or unspecified, UI) [26••]. All interventions, except hormones and periurethral bulking agents, were more effective than no treatment in achieving at least one favorable UI outcome. Among treatments used specifically for SUI, behavioral therapy was more effective than either α-adrenergic agonists or hormones in achieving cure or improvement, while α-adrenergic agonists were more effective than hormones in achieving improvement.

Phytoestrogens

Since estrogen may have some impact on urinary incontinence, it makes sense that dietary estrogens (phytoestrogens) that share biochemical similarity to estradiol may have some beneficial effect as well. There are three major classes of phytoestrogens: isoflavones (e.g., daidzein and genistein), coumestans (e.g., coumestrol), and lignans (e.g., enterodiol and enterolactone), which can function as estrogen agonists or antagonists, depending on their concentration and bioavailability in foods such as nuts, flax seed oil, soy products, and legumes [27–32].

From 2003 to 2017, there were nine published studies that evaluated the influence of phytoestrogens on the pathophysiology, symptoms, treatment, and potential prevention of UI, with four of these being animal and *in vitro* studies and the remainder clinical studies in peri- and postmenopausal women [27]. Bench studies suggested that phytoestrogen use was associated with pubocervical fascia fibroblast proliferation and improved urethral closure pressure, as well as thicker and larger mucosal area in all three segments of the urethra. Data from the five clinical studies showed some improvement in UUI indices; however, there was no significant difference noted in the reduction of SUI in one study [33]. Several of the remaining studies did not give information differentiating between UUI and SUI.

Clinical Outcomes of Pharmaceutical Agents that Modulate Neurotransmitters

The target of pharmacotherapy is increasing resistance, or closure forces of the female bladder outlet, and, as mentioned previously, there are several potential neurotransmitter targets for addressing SUI. While several pharmaceutical agents have been investigated for the treatment of female SUI, few are currently available for use. As has become common, data from RCTs are infrequently found and many of the agents have been ultimately found to be ineffective or limited by side effects. The International Consultation on Incontinence does not recommend any medications for the treatment of SUI, and no medications are currently approved by the U.S. Food and Drug Administration (FDA) for this purpose [34]. Regardless, there is continued clinical interest in their development and use.

Imipramine

Imipramine is a tricyclic antidepressant, which inhibits the reuptake of acetylcholine, dopamine, norepinephrine, and serotonin in the brain. It also acts on other receptors, such as H1 histamine receptors. Blockade of neurotransmitter reuptake leads to their increased concentration in the synaptic cleft and a longer duration of action. Imipramine's mechanism on continence is not completely understood but may be attributed to its anticholinergic effect. Its use for incontinence is currently off-label, and it has not been studied in RCTs. Blockade of the H1, α1-adrenergic, and muscarinic receptors accounts for the sedative, hypotensive, and anticholinergic effects, respectively, which may increase its side effect profile in vulnerable populations [35].

Alpha-Adrenergic Agonists

Alhasso et al. assessed 22 randomized trials encompassing 1099 women, over half of whom received an α-adrenergic agonist (phenylpropanolamine, norepinephrine, Ro 115-1240, or midodrine) [36]. There was weak evidence to suggest that use of an α-adrenergic agonist was better than placebo treatment, and there was not enough evidence to assess the

effects of adrenergic agonists when compared to, or combined with, other treatments such as estrogen. Rare, but serious, side effects such as cardiac arrhythmias and hypertension have been reported with the use of α-adrenergic agonists.

Beta-Adrenergic Agonists and Antagonists

Propranolol is a nonselective β1- and β2-adrenergic receptor antagonist with a positive impact on SUI; however, no randomized trials are available and its efficacy must be balanced against potential cardiac adverse events [15, 37]. β-Adrenergic receptor agonists may have a role in treating SUI by increasing the contractility of the striated urethral sphincter by potentiating acetylcholine at the neuromuscular junction [15]. Clenbuterol stimulates β2-adrenoceptors and has been shown to have some efficacy for SUI in two Japanese trials [38, 39]. However, a Cochrane review that assessed three randomized or quasi-randomized clenbuterol trials [36, 38–40] concluded that there was weak evidence to suggest that active treatment with any adrenergic agonist drug is better than placebo in reducing the number of pad changes and UI episodes, as well as improving subjective symptoms. Side effects of clenbuterol include tremors, arrhythmia, and headache [15].

Serotonin and Norepinephrine Reuptake Inhibitors

Serotonin and norepinephrine reuptake inhibitors (SNRIs) represent a relatively new drug class for the treatment of micturition dysfunction. The primary medication in this class, duloxetine, augments the serotonergic and noradrenergic systems by acting at the CNS level (Onuf's nucleus in the sacral spinal cord). This results in increased urethral rhabdosphincter activity which is mediated by α-1 adrenergic receptors and 5-HT2 receptors [41]. As may be expected, women randomized to 40 mg duloxetine were found to have significantly increased mean and maximal urethral closure pressure (UCP) along the entire urethra at rest increased mean UCP over the distal third of the urethra while coughing, compared to women given placebo [18]. Duloxetine is not currently FDA-approved for SUI in the USA; however, off-label use is not uncommon since this drug was FDA-approved in 2004 for treatment of major depressive disorder (Cymbalta; Eli Lilly). Duloxetine is currently only licensed for the treatment of female SUI in the European Union.

Much of the US data emerged from the Duloxetine Urinary Incontinence Study Group who conducted a double-blind, placebo-controlled study of over 600 North American women [42–44]. The group demonstrated a significant improvement in incontinence episode frequency (IEF) and overall quality of life (QoL) in women taking duloxetine, and results were similar for women with pure SUI and MUI. The main downside was the significant discontinuation rate due to adverse events (24% for duloxetine vs. 4% for placebo), with nausea the most common reason for discontinuation (6.4%).

A Cochrane review of 10 trials and 3944 adults with predominantly SUI randomized to duloxetine or placebo and/or PFMT echoed the findings above [45]. During the short treatment duration (3–12 weeks), duloxetine was significantly better than placebo in terms of QoL and perception of improvement. Individual studies demonstrated a significant (~ 50%) reduction in the IEF with duloxetine; however, meta-analysis of objective indices such as the stress pad test and pad weight change failed to demonstrate a benefit for duloxetine over placebo. As mentioned above, duloxetine use was associated with significant side effects, but they were commonly reported as acceptable. In a more-recent meta-analysis of four randomized, placebo-controlled trials, 80 mg of daily duloxetine improved the mean % change from baseline in weekly UI episodes (− 13.56%, 95% CI − 21.59% to − 5.53%) and total weekly number of UI episodes (− 2.85, 95% CI − 3.91 to − 1.78) [46]. As in previous studies, subjects receiving duloxetine had increased mean changes in incontinence-QOL scores (3.24, 95% CI 2.00 to 4.48) compared to placebo, but this finding may not be clinically significant.

While duloxetine may represent a potentially beneficial advancement in the medical treatment of SUI, Eli Lilly withdrew its New Drug Application for duloxetine hydrochloride for the treatment of SUI in January of 2005. Concerns over harmful side effects remain, including nausea, vomiting, headache, fatigue, constipation, diarrhea, anorexia, insomnia, dizziness, and somnolence. Additionally, a higher-than-expected rate of suicide attempts was observed in the open-label extensions of controlled trials of duloxetine for SUI [46]. In the meta-analysis by Maund et al., however, no serious adverse events such as suicidality, violence, or akathisia were encountered in the 958 women subjected to duloxetine therapy [46]. On the other hand, patients receiving duloxetine were five times more likely than those receiving placebo to discontinue secondary to an adverse event. With a number needed to harm of 7 (95% CI 6 to 8) for discontinuing due to an adverse event, this study concluded that the risks of duloxetine therapy for SUI outweigh the benefits.

Norepinephrine Reuptake Inhibitors

TAS-303 hydrochloride, a selective norepinephrine reuptake inhibitor (NRI) with agonistic effects on urethral α1-adrenergic receptors, has recently been investigated as a medical therapy for increasing urethral tone [47••]. Unlike duloxetine, TAS-303 has low CNS penetration and selectively inhibits peripheral norepinephrine reuptake over serotonin, dopamine, or epinephrine. By increasing only peripheral norepinephrine levels, it has been hypothesized that TAS-303 would improve SUI while minimizing or avoiding the increased psychiatric disturbances commonly associated with

elevated serotonin levels in the CNS. TAS-303 dose-dependently increased basal urethral pressure in normal rats and leak point pressure in a rat vaginal distention model, exhibiting a maximal effect comparable to duloxetine [47••]. No significant effects on immobility time were noted in rats subjected to the forced swimming test (one of the most frequently used animal models for assessing antidepressant-like effects on centrally acting antidepressants), indicating minimal CNS side effects at an effective dose for urethral function. Finally, to assess possible cardiovascular risk associated with elevated norepinephrine levels, the systolic, diastolic, and mean blood pressures, as well as heart rates of dogs treated with either TAS-303 or placebo were analyzed and also showed no significant differences.

TAS-303 therapy in women with SUI has been recently presented as a poster at the ICS Meeting in 2017 (ClinicalTrials.gov: NCT02562807) [48]. Yono et al. conducted a double-blind, single-dose placebo-controlled crossover study of TAS-303 therapy in 16 females with SUI and did not encounter any serious adverse events, significant increases in blood pressure, or abnormal urinalysis results. Although two women experienced an increase in maximal UCP by more than 10 cmH_20 after administration of 18 mg TAS-303, the overall difference in maximal UCP between women on TAS-303 and placebo was not significantly different. The researchers suggested that a phase II study with a primary endpoint of SUI symptom improvement is necessary to conclusively determine the efficacy of this drug.

Selective Androgen Receptor Modulators

Along with inadequate urethral support and coaptation, weakened pelvic floor tone is considered to be a factor leading to the development of SUI in women. It has been proposed that pelvic muscles highly enriched in androgen receptors (ARs) like the levator ani may derive benefit from PFMT, much like resistance exercises may increase muscle mass through elevations in local androgen and androgen-synthesizing enzyme levels [49–51]. Indeed, ARs have been detected at high levels throughout the pelvic floor musculature as well as in the urethral smooth muscle. Studies of hyperandrogenic states, such as obese women with polycystic ovaries or mice receiving direct testosterone administration, show improved UI frequency [52]. However, due to their low selectivity for the AR, testosterone and other naturally circulating androgens are associated with a wide range of unwanted systemic symptoms. SARMs are highly selective AR agonists that are promising for the treatment of SUI by providing anabolic effects similar to natural steroidal androgens but with fewer side effects [53, 54].

GTx-024 (enobosarm or ostarine) and GTx-027, two SARMs with similar backbones, are non-steroidal AR ligands with the ability to selectively promote increased muscle mass while avoiding interference with secondary sexual organs [54]. Ponnusamy et al. analyzed the anabolic effects of GTx-024 and GTx-027 on pelvic floor musculature in an ovariectomized mouse model with post-menopausal levels of circulating hormones [54]. Prior to treatment, these mice had elevated expression of catabolic markers and a resultant decrease in pelvic floor muscle weight; however, after 28 days of treatment with either drug, the expression of catabolic markers was inhibited and the cumulative weight of pelvic floor muscles significantly increased compared to pretreatment weight and compared to placebo.

GTx-024 is by far the most extensively studied SARM with clinical and preclinical studies in both rats and humans showing increases in total lean body mass and muscle strength. A phase II trial initiated in 2016 showed promising results for the use of enobosarm specifically for treatment of SUI in postmenopausal women [55]. Seventeen women receiving 3 mg enobosarm daily for a 12-week period all experienced a decrease in average number of reported daily stress leakage episodes by at least 50% with a mean decrease of 83%, a decrease in pad weights > 70%, and an improved QoL. Post-treatment durability is promising with no patients returning to their baseline level of incontinence at 7 months of follow-up and continued benefit in the six subjects who completed 40 weeks of follow-up. No adverse events were encountered in this study.

A large placebo-controlled trial has been initiated to further assess the safety and efficacy of this drug [56]. The Assessing Enobosarm for Stress Urinary Incontinence Disorder (ASTRID) Trial enrolled 493 women at 62 centers across the USA and completed in September of 2018. Preliminary indications are that the trial did not achieve statistical significance on the primary endpoint of the proportion of patients with a > 50% reduction in daily UI episodes as compared to placebo [57]. The percentage of patients with a > 50% reduction after 12 weeks of enobosarm treatment was 58.9% for 3 mg, 57.7% for 1 mg and 52.7% for placebo. Enobosarm was generally safe and well tolerated and reported adverse events were minimal and similar across all treatment groups.

Conclusions

Medical management of SUI is an intriguing proposition owing to the abundance of receptors for hormones and neurotransmitters in the pelvic floor, bladder, vagina, and urethra. While numerous drugs have been investigated, their widespread incorporation into the treatment algorithm has been derailed by concerns over clinical improvement in symptoms, durability, and adverse event profiles. At present, none are FDA-approved for SUI. Vaginal estrogen appears to decrease overactive bladder symptoms in postmenopausal women, while systemic estrogen supplementation may be associated

with worsening symptoms. The impact of topical estrogen on SUI is inconsistent. Hence, the use of topical estrogen should continue to be used for symptoms associated with vulvovaginal atrophy and any concomitant improvement in any storage urinary symptoms considered fortuitous, albeit unexpected. Phytoestrogens have shown some potential benefit in bench studies, but clinical impact has been minimal. There is weak evidence to suggest that any adrenergic agonist is better than placebo in improving objective incontinence measures, and both alpha- and beta-adrenergic agonists are associated with significant potential for serious side effects. Available evidence suggests that duloxetine (a SNRI) can significantly improve the QoL in women with SUI, but it is unclear whether or not benefits are sustainable. Additionally, its side effects are common and may have precluded the FDA approval of this medicine. Evidence for the use of TAS-303, a NRI, is currently in the early stages and its clinically significant improvement and durability are unknown at this time. SARMs have shown promise in both animal and early human studies; however, a recent, preliminary report from a large, multi-institutional, placebo-controlled trial of enobosarm reported that this drug did not achieve statistical significance in its primary endpoint compared to placebo. On the other hand, the drug was well tolerated.

In summary, despite a lengthy history of attempts at treating SUI with pharmaceutical options, this tack remains in its infancy. The majority of drugs available for SUI treatment are associated with limited improvement, unknown durability, and high potential for significant side effects. While there is some evidence for efficacy of both SNRIs and SARMs, more research is needed. At present, none of these pharmaceutical options are FDA-approved and their use for SUI remains strictly off-label in the USA.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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