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Lower Urinary Tract Symptoms (LUTS) and Sexual Dysfunction (SD): New Targets for New Combination Therapies?

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1. Introduction

Lower urinary tract symptoms (LUTS) related to benign prostatic hyperplasia (BPH) and sexual dysfunction (SD) are highly prevalent in men over the age of 50 yr [1]. Both conditions have a significant impact on overall quality of life.

Several recent analyses [1–4] strongly suggest that although age is an independent risk factor for both LUTS and SD, LUTS is also an independent risk factor for SD. In this field, it is more correct to answer the question in terms of SD rather than only in terms of erectile dysfunction (ED): male SD may manifest as decreased libido, ejaculation dysfunction, ED, or a combination of all three conditions.

Moreover, treatment of LUTS and BPH includes pharmacologic, minimally invasive, and surgical therapies that could have an impact on sexual function. In particular, α_1-adrenergic receptor antagonists are used for the treatment of LUTS; they may affect sexual function and for some of these drugs a positive effect on SD has been reported [5–7].

Combination therapy with 5α-reductase inhibitors and α_1-adrenergic receptor antagonists has been considered the best pharmacologic therapy to reduce the risk of BPH progression, either in terms of prostate growth, or LUTS progression, or complication development. BPH and related LUTS are a complex problem where different factors influence their development and progression. Therefore, the pharmacologic approach must be also complex, including the different aspects that are related to LUTS and BPH.

Phosphodiesterase type 5 (PDE5) inhibitors are considered the first-line therapy for ED [8]. Recently some studies considered advantages and risks of a combination therapy with α_1-adrenergic receptor antagonists and PDE5 inhibitors [8–10].

Considering the high prevalence of both LUTS and SD in men over the age of 50 yr and the possible relationships between these two aspects, new combined pharmacologic approaches targeting these two aspects should be investigated.

2. New data indicate a potential link between LUTS and SD

As underlined by McVary et al [2], a casual association between LUTS and SD cannot be established only on the basis of epidemiologic studies. Reports should analyse the strength of the association, the presence of a level response effect (more LUTS = more SD), and a temporal relationship (one may precede the other). The relevance of this analysis is underlined by the potentiality of new clinical targets and therapeutic options.

Overall, 52% of men aged 40–70 yr have some degree of SD, and two thirds of these men have moderate to severe LUTS [2]. Also the prevalence of

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BPH progressively increases from the fourth (8%) to the eighth (82%) decade of life [2]. Similarly LUTS related to BPH increase in incidence with age [2]. Community-based studies underlined that sexual satisfaction negatively correlates with increasing age and LUTS [3]. The relative risk of sexual dissatisfaction stratified by the International Symptom Score (IPSS) ranged in these studies [2,3] from 1.0 with an IPSS of 0–3.3 with an IPSS $>$ 19. Other studies found a linear relationship between LUTS and increasing risk of SD [4].

The relationship between LUTS and SD is also relevant in terms of quality-of-life assessment. It is well known that both LUTS and SD significantly affect the quality of life of patients, and therefore, a direct relationship between these two aspects must also be considered in terms of global effect on quality of life.

As supported by different studies [2], the link between LUTS and SD may have basic science supports. Possible biologic explanations fall into different categories or theories, [2], in particular on a possible relationship between nitric oxide synthase/nitric oxide level that decreases in the prostate and penile smooth muscle.

3. Impact of α_1-adrenergic antagonist therapy for LUTS on SD

The α_1-adrenergic antagonists in combination with 5α-reductase inhibitors represent the pharmacologic options for the treatment of LUTS related to BPH. Because treatment options for managing BPH have different effects on sexuality, the sexual dimension should be considered when assessing the patient's expectations and the choice of treatment.

The α_1-adrenergic antagonists as treatment of LUTS can affect sexual function of the patient. The α_1-adrenoceptor blockers (alfuzosin, doxazosin, tamsulosin, terazosin) show an incidence of decreased libido and ED closely similar to placebo, but differ in their impact on ejaculation, tamsulosin being associated with a higher incidence of ejaculation dysfunction (10%) than other α_1-adrenoceptor blockers (0–1%) and placebo (1%), which is unrelated to retrograde ejaculation [5]. A randomised, placebo-controlled, crossover study conducted in healthy volunteers showed that tamsulosin 0.8 mg once daily markedly decreased mean ejaculate volume in almost 90% of men, with 35% having no ejaculation. By contrast, there was no lack of ejaculation in subjects receiving 10 mg alfuzosin once daily or placebo. Sperm concentrations in urine after ejaculation were similar for the different treatment groups, confirming that the ejaculatory dysfunction with tamsulosin was unrelated to retrograde ejaculation. It may be related to a peripheral effect on seminal vesicles or the vas deferens. A central effect is also plausible because tamsulosin shows a strong affinity for 5-hydroxytryptamine 1A- and D2-like receptors, both of which are involved in the central command of ejaculation [5].

On the other hand, other aspects positively link α_1-adrenergic antagonists with the treatment of SD. The α_1-adrenergic antagonists may contribute to the improvement of SD, in particular of ED, through α-adrenergic mechanisms that may cause alterations in the balance of penile vasoconstrictive and vasorelaxant forces that favour pro-erectile mechanisms [2]. As of now, reports detailing this positive relationship between α_1-adrenergic antagonist treatment and improvement of SD remain few and must be improved. Demir et al [6] showed that the contractility of human corpus cavernosum is increased in the presence of bladder outlet obstruction (BOO). Doxazosin generates effective corpus cavernosum smooth muscle relaxation in the presence of BOO. Other studies [7] showed that in patients with LUTS treated with alfuzosin, self-perceived sense of sexual satisfaction was significantly improved from baseline, with the degree of improvement correlated with age.

4. Combination therapy with α_1-adrenergic antagonist and PDE5 inhibitors

The hypothesis of a causal association between LUTS and SD and the possible related biologic mechanism produced hypotheses for new combination therapies in our patients. Kaplan et al [8] investigated the synergistic effect of doxazosin and intracavernosal injection (ICI) therapy in patients for whom ICI therapy alone failed to induce an erection. Overall, in a limited population, 57.9% of patients with the combined regimen had a significant therapeutic response (>60% International Index of Erectile Function [IIEF] improvement).

Some authors [9] suggested comorbid LUTS and SD should be treated with an α_1-androgen receptor antagonist and PDE5 inhibitor combination therapy. The combination of a PDE5 inhibitor may have beneficial effects either in terms of LUTS or in terms of SD. In terms of SD, the combination of a PDE5 inhibitor may support the hypothesised positive effect of an α_1-adrenergic antagonist on SD but also minimises the possible negative effect of α_1-blocker on SD. The hypothesis of this combination therapy is also supported by some evidence regarding a

possible positive effect of PDE5 inhibitors on LUTS [9].

Recently Kaplan et al [10] analysed the efficacy and safety of alfuzosin 10 mg once daily, sildenafil 25 mg once daily, and the combination of both on 62 patients with LUTS suggestive of BPH and ED. Men aged 50–76 yr with previously untreated LUTS and ED were randomised to the three treatments. Results were analysed in terms of IPSS, urinary flow rates, postvoid residual urine (PVRU) volume, and IIEF assessment at week 12. The author underlined that improvement of IPSS was significant with all three treatments but greatest with the combination (24.1%) when compared to alfuzosin (15.6%) and sildenafil (16.9%) alone. Maximum urinary flow rate and PVRU were significantly improved with alfuzosin alone or the combination. Improvement in IIEF was slight with alfuzosin alone (16.7%), marked with sildenafil (49.7%), and greatest with the combination (58.6%). Dropout from the study because of adverse events was reported in 11% of cases: two men in the alfuzosin group (dizziness), two in the sildenafil group (flushing, dyspepsia), and three in the combination group (dizziness, gastric upset). No serious adverse events were reported. The author concluded that the combination of alfuzosin and sildenafil is safe and more effective than monotherapies to improve both LUTS and ED.

This is an interesting report but no conclusions in this field can be obtained from this analysis. This represents only a pilot study on a limited population and without a placebo control. In particular, the lack of a placebo control and the limited period of analysis both reduce the clinical significance of this study. However, these data can support larger multicentric, placebo-controlled, and long-term studies analysing the safety and efficacy of this combination therapy in treating both LUTS and SD.

In particular, the possibility of vasodilatory adverse events associated with the combination of these two classes of drugs must be carefully analysed in the long term.

5. Conclusions

As the prevalence of both SD and LUTS increases with age, physicians could manage these two conditions simultaneously. Moreover, medical therapies for either one of these conditions can affect the other and this should be carefully considered when making treatment decisions [9]. Nitric oxide is an important mediator of the relaxation of bladder and urethral smooth muscle and could modulate prostatic smooth muscle tone. PDE5 inhibitors can therefore have a positive impact on both SD and LUTS and could be considered in combination with all pharmacologic options for LUTS and BPH. Although placebo-controlled and long-term studies are needed to confirm the impact and safety of these new pharmacologic combination strategies, on both SD and LUTS, this reinforces the need for a common approach to managing these two highly prevalent and bothersome conditions.

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