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review

Coadministration of low-dose serotonin/noradrenaline reuptake inhibitor (SNRI) duloxetine with α_2-adrenoceptor blockers to treat both female and male mild-to-moderate stress urinary incontinence (SUI)

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SUMMARY: **Coadministration of low-dose serotonin/noradrenaline reuptake inhibitor (SNRI) duloxetine with α_2-adrenoceptor blockers to treat both female and male mild-to-moderate stress urinary incontinence (SUI).**

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Background. *Female urinary incontinence is a relatively common disorder affecting women in different age groups, with significant prevalence amounts of stress-related subtype (stress urinary incontinence, SUI). Various neurotransmitters/neuromodulators - particularly both the glutamatergic and GABA-ergic ones - are involved in micturition/urinary continence nerve centre-based control, where Onuf's nucleus plays an important functional role under the adiuvant serotoninergic/noradrenergic influences.*

Objectives. *To outline, deriving them from the literature review, the SUI therapeutic implications of SNRI (serotonin-noradrenaline reuptake inhibitors) particularly of the duloxetine, though displaying its full therapeutic dose (40 mg twice/day)-related side effects and, therefore, highlighting recent issues concerning novel drug administration modalities to avoid such adverse events.*

Emerging knowledges. *Intriguing studies in SUI animal models have shown that co-administration of duloxetine low dose with α_2-adrenoceptor antagonists - given the α_2-adrenoceptor inhibition-induced enhancement of duloxetine effectiveness on the urethral rhabdosphincter - can avoid the duloxetine-related adverse events though perspectively reaching, in perspective translational clinical applications, the awaited beneficial effects for women suffering from intrinsic rhabdosphincter deficiency-based mild-to-moderate SUI as well as, in men, to treat post-prostatectomy mild SUI.*

KEY WORDS: Duloxetine - Neuropharmacology - Prostate - Urethral rhabdosphincter.

Introduction

Urinary incontinence (UI) - inability to willingly control bladder voiding - is a relatively common disorder, affecting women in different age groups, whose median prevalence, indeed, widely ranges from 20% to 50% depending on its various appraisals (1-9).

On the basis of the literature data (1-4, 10), it has to be pointed out that, compared to the old definition of U.I. (International Continence Society, ICS, 1988) - as «a condition where involuntary loss of urine is a social/hygienic problem, objectively demonstrable» - the more recent one (ICS, 2003) - as «the complaint of any involuntary leakage of urine» - by uncoupling the significance of this disorder from related socio-sanitary implications, may allow about it a better epidemiologic assessment. Nevertheless, U.I./pelvic floor dysfunction-related conditions still escape an unequivocal definition, considering that the current terminology quite includes over 250 different conceptual wordings (1), what gives pertaining reasons for continually occurring new U.I. assessments guideline proposals (2).

A better U.I. epidemiologic rating refers to prevalence of various U.I. typologies, where *pure stress urinary incontinence* (SUI) reaches 33.8% of U.I. total amount, in comparison with the *pure urge one* (31.8%) and that *mixed* (34.4%) (10).

Overactive bladder-dependent urge incontinence has been excluded from this article, its drug therapy particularly consisting of either antimuscarinic agents - including oxybutynin, tolterodine, darifenacin, solifenacin, trospium, propiverine (with calcium-antagonist properties too) - and β_3-adrenoceptor agonists, such as mirabegron, or intravesical use of capsaicin-analog resiniferatoxin or even into-bladder muscle cystoscopic injection of Botulinum toxin (onabotulinum-toxin A, Botox).

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Neurotransmitters involved in urinary continence/guarding reflex

Pontine micturition centre, PMC (Barrington's nucleus, located on pontine medial region, M-region) and *pontine storage centre*, PSC (located on pontine lateral region, L-region), though anatomically not-interconnected at the brainstem level, play, by their projections to the spinal cord, a coordinated functional central control on both micturition and urinary continence, with the additional involvement of the forebrain (anterior cingulate gyrus, preoptic/hypotalamic area, amigdala) and the cerebral cortex (dorsolateral prefrontal cortex, whose activation, during the bladder voiding, has been shown by both PET (positron emission tomography) and fMR (functional magnetic resonance) human studies (8, 11-15).

The excitatory *PSC projection*, by glutamatergic signalling, spreads to the sacral motoneurons - nucleus of Onuf - directed to pelvic floor, including both urethral and anal rhabdosphincters, thus resulting in sequentially somatic pudendal acetylcholine-releasing nerve/muscle nicotinic receptor-mediated contraction of urethral rhabdosphincter, with consequent increase in urethral pressure as the *continence circuit* end (11). The glutamate, an essential excitatory brainstem/spinal neurotransmitter to support the urinary continence/guarding reflex, mediates the generation of action potentials in the sacral rhabdosphincter motoneurons, by binding NMDA (N-methyl-D-aspartate)- and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid)-receptors (13, 16, 18).

The *PMC activation*, instead, projects, via -aminobutyric acid (GABA)-ergic pathway, into the intermediolateral sacral columnae, where inducing, by an inhibitory interneuronal mechanism, the relaxation of the external urethral sphincter (*micturition circuit*) (11-18).

To go into some details, the bladder filling-induced by vesical wall mechanoreceptor stimulation, besides the somatic pudendal-nerve-cholinergic pathway-mediated rhabdosphincter contraction, simultaneously promotes an activation of the sympathetic adrenergic pathway that, via hypogastric nerves, reaches the -adrenoceptor (mainly, the α_{1A}-subtype) of smooth muscle urethral sphyncter. Between such dual, somatic and autonomic-sympathetic, neuronal mechanism directed to increase urethral pressure, that somatic plays the main role - guarding reflex - when, because of sudden increased in intra-abdominal pressure (sneezing, coughing, laughing), also the intravesical pressure passively rises (19, 20). The PSC-proper glutamatergic signal appears to be the essential spinal «on-off-switch» regarding the rhabdosphincter activity, given that additional neuromodulators - serotonin (5-TH), arising from raphe nucleus, and noradrenaline (NA), from locus coeruleous - are inadequate to act on Onuf's motor neurones without their preliminary glutamate-mediated sensibilization (11-18, 21).

The Onuf's nucleus - placed in the ventral born of sacral spinal cord (1°-3° segment) - is a specialized group of motoneurons, whose histochemical studies show autonomic system-related neuropeptide constitution (high concentration of opioids such as enkephalins) whereas their network - mutual connection by dendrodendritic gap junctions - resembles a somatic input modality to allow a massive activation of the rhabdosphincter with following its fast contraction (22). As for Onuf's nucleus-proper *serotoninergic receptor subtype* involvement to strengthen the rhabdosphincter activity, 5-HT_{1A} receptors seem to prevail, though also 5-HT_{2C}-and 5-HT_3 adrenoceptors may become effective (14, 23, 24). With regard to Onuf's nucleus *noradrenergic receptor subtypes*, the α_1-adrenoceptors play an important role on adjuvantly boosting the glutamate-mediated activation of somatic motoneurons directed to rhabdosphincter, moreover considering that α_1-adrenoceptor-mediated *symphatetic* mechanisms are involved, by themselves, in the contraction of smooth muscle urethral sphincter, while the α_2-adrenoceptor ones showing opposite effects (sphincterial relaxation), so that the α_2-adrenoceptor blockers atipamezole and rauwolscine can induce an increase in urethral sphincter contraction (14, 20, 23). It follows that, during the storage phase, besides the main action of glutamate on the Onuf's nucleus, the additional contribution of both noradrenaline and serotonin neuromodulators enhances the glutamate-mediated activation of somatic pudendal motoneurons that, in turn, induce the acetylcholine-mediated stimulation of the rhabdosphincter-nicotinic receptors, thus allowing a stronger sphincterial response (11-21, 25).

Going now from the continence circuit to the micturition one, the PMC stimulation induces, via GABA neurons, a inhibitory modulation on both dorsal gray commissure of the sacral cord and Onuf's nucleus motoneuron-GABA receptors, hence, an immediate relaxation of the urethral rhabdosphincter simultaneously with contraction of the bladder detrusor muscle (11-21, 23-25).

Impact of serotonin/noradrenaline reuptake inhibitors on urethral rhabdosphincter activity

The strengthening of urethral resistance to bladder outlet may be reached by different pharmacological measures: a) stimulation of sympathetic pathway

TABLE 1 - CONTINENCE MECHANISM-RELATED MANAGEMENT OF FEMALE STRESS URINARY INCONTINENCE.

Physiology

Urinary continence mechanisms during sudden elevation of intraabdominal pressure

Passive closure mechanism
due to instant transmission
of intraabdominal pressure to the bladder neck
and proximal urethra[40]

Active closure mechanism
due to neurally-mediated
urethral rhabdosphincter contraction reflex
elicited by sudden pelvic floor stress[40]

Pathophysiology

Anatomical SUI
Displacement of bladder neck
off the abdominal pressure area
(bladder neck/urethral hypermobility)

Dysfunctional SUI
Intrinsic rhabdosphincter deficiency
Neural disorders affecting
the guarding reflex

Management

Surgery
Cysto-urethral junction
reposition in intraabdominal area
(open cysto-colpo-suspension,
suburethral tension-free tape procedures)

Conservative approaches
Drug therapy
SNRI
Low-dose SNRI + α_2-adrenoceptor blockers

Minimally invasive treatments
Transurethral injection of bulking agents
(collagen, hyaluronic acid, polyacry-
lamide hydrogel, autologous fat)
to create a grummet around the
bladder neck and/or mid-urethra [41]

← When the drug therapy fails

Bio-integrative measures to restore sphincteric function
Intrarhabdosphincter injection of autologous
either striated muscle-derived cells or stem cells

Additional therapy measures: lifestyle/behavioral changes, pelvic floor re-education and/or electro/magneto-stimulation, biofeedback (29, 32, 41).

to proximal smooth muscle-α_1-adrenoceptors; b) direct activation of rhabdosphincter-acetylcholine/nicotinic receptors; c) direct stimulation of Onuf's nucleus glutamate receptors to boost somatic-pudendal pathway to rhabdosphincter; d) enhancement, as quite pertaining to the matter of this paper, of the glutamatergic effects of Onuf's nucleus, by there increasing the serotonin/noradrenaline availability. In this respect, indeed, the serotonin/noradrenaline reuptake inhibitors (SNRI) at the Onuf's nucleus (presynaptic level of pudendal motoneurons), can cause additional excitatory effects on previously glutamate-sensitized somatic pudendal motoneurons directed to urethral rhabdosphincter so that improve the storage reflex particularly in response to sudden increases in bladder pressure (guarding/continence reflex) (8, 9, 11-21, 23-31).

Duloxetine, a potent balanced inhibitor of both serotonin/noradrenaline reuptake, can induce, via above mechanisms-mediated boost of urethral rhabdosphincter performance, an improved bladder urine storage, together with facilitating the vesical wall relaxation by directly binding its 5-HT_1 receptors (6, 8, 9, 23, 25-31). The effects of duloxetine on the urethral sphincter are blocked by LY53857 and prazosin, respectively 5-HT_2 serotoninergic and α_1-adrenergic

receptor-antagonists that, instead, are unable to reverse 5-HT_1 receptor-mediated effects of duloxetine on the bladder distension and capacity (23, 25, 32).

Depending on *PMC activation*, the GABA-ergic inhibitory effects on glutamate tone (glutamate tone withdrawal) at Onuf's nucleus-proper post-junctional pudendal motoneurons, make there vain the duloxetine-induced potential of serotonin and noradrenaline, thus allowing rhabdosphincter relaxation, hence the bladder emptying (9, 23, 25, 30).

Similar to duloxetine, SNRI *venlafaxine* can increase rhabdosphincterial electromyografic (EMG) activity, that's reversed by the α_1-adrenoceptor selective/5-HT nonselective antagonist methiothepin, but larger doses of such SNRI are required to obtain the same effectiveness of duloxetine. Co-administration of S-*norfluoxetine*, a selective serotonin reuptake inhibitor, and *thionisoxetine*, a selective noradrenaline reuptake inhibitor, unexpectedly has no boosting effects on urethral rhabdosphincter (12, 21, 25).

Unfortunately duloxetine, although clinically efficacious, besides towards the patients suffering from either deep depression/anxiety disorders or diabetic neuropathy and fibromyalgia, also to treat women with SUI, however, because of its *side-effects* - such as nausea, dry mouth, dizziness, insomnia, sometimes instead sonnolence, fatigue, headache - is so far approved, as therapeutic measure for SUI, only in Europe but not in USA (20, 32, 33).

Emerging SUI pharmacotherapy by SNRI/α_2-adrenoceptor blocker co-administration

Considering that the therapeutic dose of duloxetine to treat SUI (40 mg, twice a day) is frequently associated with above-mentioned side-effects, it has been shown, in SUI animal models, that the dose may be significantly reduced when such drug is co-administered with α_2-*adrenoceptor antagonists* (yohimbine, idazoxan), given that the α_2-adrenoceptor inhibition can boost the effects of duloxetine on the urethral rhabdosphincter. It follows that, together with avoiding or at least mitigating the duloxetine-related side-effects, the sneeze-induced guarding reflex might be effectively supported by this dual drug co-administration (20, 34).

Regarding the possible affinity of α_2-adrenoceptor blockers, yohimbine and idazoxan, for the imidazoline receptors, recent studies reveal not interactions between yohimbine and imidazole receptors, though with enhancement of low-dose duloxetine effects, while idazoxan, endowed with the same effectiveness on SUI, has equal binding affinity for both α_2-adrenoceptors and imidazole (19, 20, 26, 35).

So, efficacious synergistic effects, in SUI animal models, due to co-administration of low-dose duloxetine and α_2-adrenergic blockers, allow to propose such drug combination, as a novel therapeutic measure, to boost the clinical effectiveness of low-dose SNRI$_S$ in women suffering from SUI depending on intrinsic rhabdosphincter deficiency meanwhile avoiding the duloxetine-related side-effects (20) (Table 1).

Novel potential drugs for SUI are identified with pyrimido (4,5d) azepines that, as potent selective 5-HT_{2C} receptor agonists, have shown a strong efficacy in preclinical canine model of SUI (36).

Some smooth urethral sphincter α1-adrenoceptors mainly targeting drugs

Novel potential pharmacotherapy secondary measures for SUI focus on the use of various drugs including: a) RO 115-1240 (sulphonamidoaryl-functionalized imidazoline) which, as a potent selective urethral smooth muscle-proper $\alpha_{1A/1L}$-adrenoceptor partial agonist, can improve the symptoms of SUI with no or little α_1-adrenoceptor cardiovascular stimulation whereas a novel selective α_{1A}-adrenoceptor partial agonist PF-3374076 [2-(R-5-Cl-4-methoxymethylindan-1-yl)-1H-imidazole], though inducing, via a central nervous influence, a favourable urethral contraction response, unfortunately causes cardiovascular side-effects (37, 38); b) PSD 503, a adrenergic agonist phenylephrine 20% topical gel, for vaginal applications close to area of the urethral sphincter, that, though resulting well tolerated from phase-II multicentre clinical studies and whilst objectively effective to treat SUI, is charged, instead, of questionable acceptability in the practice (39).

Such drugs, as mainly acting on smooth muscle sphincter simpathetic neuroceptors, little or no share in the properly urethral rhabdosphincter mechanism-related guarding reflex (40, 41).

Pharmacotherapy for prostatectomy-related mild-to-moderate SUI

So far, the efficacy of duloxetine has been poorly evaluated in the management of male SUI, that is most commonly due to iatrogenically (after radical prostatectomy) or, more rarely, to traumatically (disruption of pelvic muscle floor) - induced inefficiency of external urethral sphincter.

Prostatectomy-related SUI impairs the quality of

life of patients, particularly affecting the so-called "social continence", as ability to participate, without any limitation, to normal social activities (42).

To treat prostatectomy-induced mild-to-moderate urinary incontinence, various conservative measures may be suggested, such as pelvic floor training, biofeedback, both electrical and magnetic field stimulation, and/or pharmacotherapy by administration of SNRI *duloxetine* (80 mg daily). This drug, as it has been above explained with regard to female SUI, can improve the urinary continence by inducing, on the one hand, the relaxation of the detrusor muscle - sometime associating it with antimuscarinic drugs or β_3-adrenoceptor agonist mirabegron, when SUI coexists with urge incontinence - and by increasing, on the other hand, the tone of urethral smooth muscle sphincter together with particularly boosting the guarding reflex-related, Onuf's nucleus-mediated, contraction of the urethral rhabdosphincter (42-44).

It is to be expected that also for postprostatectomy-SUI patients, the co-administration of low dose-duloxetine with *α_2-adrenoceptor antagonists* might favourably avoid or, at least, mitigate the above-mentioned duloxetine-related adverse effects.

If such conservative measures result ineffective - what in case of serious postprostatectomy SUI - different surgical procedures may be applied, rancing from minimally invasive techniques, such as paraurethral injection therapy (submucosal injection of " bulking agents", that unfortunately may sometimes cause an inflammatory reaction-induced impairment of urethral elasticity, *i.e.* "frozen urethra"), suburethral sling, to implantation of either pro-Act device or, as a drastic measure, Ams 800 artificial urinary sphincter (42).

Current research endeavours and future outlooks

The ability of duloxetine to strengthen, by promoting neuromodulator properties of serotonin and noradrenaline at the level of guarding reflex-related central nervous structures, the contraction activity of pelvic floor muscle/urethral rhabdosphincter, so enhancing intrinsic urethral pressure and bladder outlet resistance, particularly during abrupt increases of abdominal pressure (guarding reflex), allows to it define as a beneficial drug option for women suffering from *intrinsic rhabdosphincter deficiency-based*, mild-to-moderate, SUI (6, 8, 9, 26-34) (Table 1).

Unfortunately, the duloxetine therapeutic dose (40 mg bid)-depending possible adverse events - among whose some related to central nervous system such as dizziness, insomnia, sometimes sonnolence, headache, fatigue while others to gastroenteric tract such as anorexia, nausea, mouth dry, constipation - have driven the researchers to intriguingly develop new drugs that, when co-administration with duloxetine, allow to reduce its dose, so avoiding its side-effects. Regarding it, the α_2-adrenoceptor antagonists, by increasing, via central nervous-based mechanisms, the duloxetine effects on urethral rhabdosphincter, may be an attractive chance for their co-administration with duloxetine low-dose (19, 20, 34, 35).

Further developments of the research are directed to focus on more thorough studies involved in the contraction mechanisms of the urethral rhabdosphincter, in order to identify new drugs that, better targeting specific neurotransmitters and neuromodulators, might improve sphincterial efficiency, particularly during the continence reflex.

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