

Tolerability of Amine Uptake Inhibitors in Urologic Diseases

Martin C. Michel*, Henricus G. Ruhe, Annemieke A. de Groot, Ramiro Castro and Matthias Oelke

¹*Depts. of Pharmacology & Pharmacotherapy, Psychiatry and Urology, Academic Medical Centre, University of Amsterdam, Meibergdreef 15, 1105 AZ Amsterdam, The Netherlands*

²*CD Medical Affairs, Boehringer Ingelheim, 55216 Ingelheim, Germany*

Abstract: Inhibitors of serotonin (5-HT) and/or noradrenaline (NA) reuptake have been developed for pharmacological treatment of major depressive disorder. Insights in the role of 5-HT and NA in the neurological control of the lower urinary tract have also led to their application in common urological conditions such as stress urinary incontinence (SUI), nocturnal enuresis and ejaculatory disorders.

The European approval of the 5-HT and NA reuptake inhibitor (SNRI) duloxetine for treatment of SUI underlines the importance of a new approach in SUI, but has also given rise to questions about the safety of antidepressants in urology. This paper reviews the safety of 5-HT and NA reuptake inhibitors in their on- and off-label use in urology. A systematic Medline search was performed for randomised controlled trials, meta-analyses and practice guidelines dealing with antidepressants in urology. The safety profiles of the drugs in the urological population were compared with data from psychiatric populations.

Tricyclic antidepressants are associated with serious cardiovascular side effects. In addition, anticholinergic and antihistaminic side effects are common. Although recently questions have been raised regarding the cardiovascular safety profile of venlafaxine, most selective 5-HT reuptake inhibitors and SNRI have not been associated with serious cardiovascular effects. Their most common side effect is nausea. However, nausea tends to be mild and, importantly, transient. Patient counselling about side effects and up-titrating doses may be useful strategies for minimising discomfort and withdrawals.

Keywords: Neurotransmitter uptake inhibitors, antidepressive agents, urological diseases, sex disorders.

INTRODUCTION

Amine uptake inhibitors, including tricyclic antidepressants (TCA), selective serotonin (5-HT) reuptake inhibitors (SSRI) and dual 5-HT and noradrenaline (NA) reuptake inhibitors (SNRI) have primarily been developed for the treatment of major depressive disorder (MDD). These drugs act through increasing the availability and the activity of the monoamine neurotransmitters 5-HT and/or NA in the synaptic cleft. In addition, some of these agents may also block the reuptake of the monoamine neurotransmitter dopamine. The rationale for the efficacy of these agents in the treatment of depression is based on the monoamine hypothesis, stating that a deficiency in one or more of the brain monoamines (e.g. NA, 5-HT, dopamine) leads to the development of clinical depression; antidepressive agents increase NA, 5-HT and/or dopamine-mediated neurotransmission [1].

Besides their involvement in the regulation of mood and emotions, the role of the neurotransmitters 5-HT and NA has also been established in several other body functions such as the modulation of pain perception, the enteric nervous system, and the control of the lower urinary tract. The role of TCA and SNRI in the treatment of chronic - particularly neuropathic - pain has been established in randomised clinical trials [2,3]. In contrast, SSRI are apparently less

effective in alleviating pain symptoms, which might be related to their lack of effect on NA reuptake [4,5].

TCA, SSRI and SNRI are also applied in the urological and urogenital setting, particularly in the treatment of incontinence, nocturnal enuresis and ejaculatory disorders. However, not all of these applications have an official approval. The TCA imipramine has been used off-label for treating female stress urinary incontinence (SUI) [6]. Both imipramine and another TCA, desipramine, are recommended as pharmacological treatment for retrograde ejaculation in the EAU guidelines on ejaculatory disorders [7]. Furthermore, SSRI have been applied in the treatment of premature ejaculation (PE) [8,9], but they are not officially approved for treating the condition. SNRI have also been tested for the treatment of PE but seem to be less effective [10].

The on-label use of amine uptake inhibitors in the urological setting comprises the TCA imipramine for treating nocturnal enuresis in children as well as the SNRI duloxetine in female SUI. Duloxetine was approved for treating SUI in women by the European Medicines Agency (EMA) in August 2004 [11]. The approval of duloxetine and its incorporation in the 3rd International Consultation on Incontinence (Monaco 2004) guidelines as a suitable conservative therapy with level 1 evidence and grade A recommendation [12] highlight the role of the neuro-urological control in the management of lower urinary tract symptoms. However, questions remain within the urological community as to the safety of these types of drugs.

*Address correspondence to this author at the Dept. of Pharmacology & Pharmacotherapy, Academic Medical Centre, University of Amsterdam, Meibergdreef 15, 1105 AZ Amsterdam, The Netherlands; Tel: + 31 20 566 6762; Fax: + 31 20 696 596; E-mail: m.c.michel@amc.uva.nl

In this review we focus, therefore, on the application and tolerability of TCA, SSRI and SNRI in the urological and male urogenital setting. An overview of randomised controlled trials, meta-analyses and practice guidelines for the on- and off-label use of these amine uptake inhibitors in urology is provided, and the mode of action is discussed in order to provide a rationale for their use in this field. Subsequently, we discuss the safety and side effect profile in non-psychiatric populations suffering from non-life threatening urological and urogenital conditions, and put these in perspective through comparing it with the safety profile that has been reported from the use of these drugs in the psychiatric setting.

METHODS

A systematic search of the Medline database from 1966 to April 2005 was carried out of published randomised controlled (RCT) trials, meta-analyses and practice guidelines related to the use, pharmacological action and safety of amine neurotransmitter uptake inhibitors applied in urological, including sex disorders. The Medline indexed search terms “neurotransmitter uptake inhibitors” or “antidepressive agents” were combined with “urologic diseases” or “sex disorders”. The search results were limited to studies in humans, reported in English language. References of the retrieved papers were manually searched for additional papers dealing with the application of SNRI, TCA or SSRI in the field of urology.

These search results were completed with an indexed Medline search on the substance names of the antidepressant agents that came out from the previous searches, applying the same search limits (English language, human beings, and RCT, meta-analysis or practice guidelines).

Subsequently, a search of the Cochrane library was performed using the key words “enuresis”, “stress urinary incontinence”, or “ejaculation/ejaculatory”. The reference lists of selected review papers were also checked for additional references.

As next step, in order to obtain safety information in psychiatric populations, the Medline database was searched for meta-analyses related to the side effect profile of amine uptake inhibitors in the psychiatric setting. This search used the MESH headings: “neurotransmitter uptake inhibitors” or “antidepressive agents” focusing on pharmacological action and adverse effects in humans.

Furthermore, the websites of the European Urological Association (EAU) and the American Association of Urology (AUA) were searched for practice guidelines involving the use of amine uptake inhibitors in the urological setting.

Finally, the product information sheets of the amine uptake inhibitors used in urology and available *via* the website of the Food and Drug Administration (FDA) and the Physician’s Desk Reference (PDR), a complete list of medication available on prescription in the US, were searched for drug safety information. It should be noted that some additional information may exist outside the public domain, e.g. in proprietary databases of companies manufacturing such drugs; the lack of access to such databases is a possible limitation of the current analysis.

Moreover, it should be noted that our search strategy had been limited to RCTs. While these have the greatest power to discriminate drug effects from placebo effects, their size and list of inclusion and exclusion criteria limit the extrapolation of their results to a real-life situation.

RESULTS

The search results revealed three main domains in urologic and urogenital disorders in which amine uptake inhibitors are being used: SUI, nocturnal enuresis in children, and PE. Other domains include the treatment of overactive bladder, interstitial cystitis, retrograde ejaculation and erectile dysfunction (ED). For the ease of classification, an overview of the retrieved RCT is presented, split up into Table 1 (SUI, enuresis, urgency and overactive bladder) and Table 2 (PE and ED).

Urologic Diseases

The focused searches revealed a total of 12 RCT dealing with the use of duloxetine in SUI [13-18], amitriptyline in interstitial cystitis [19], imipramine and mianserin in nocturnal enuresis [20-23], and imipramine in overactive bladder [24]. One reference comprised the South African practice guidelines of the management of nocturnal enuresis [25].

Sex Disorders

The search yielded a total of 17 RCT discussing the application of amine uptake inhibitors in sex disorders. Thirteen of these reported on the pharmacological management of PE, for which sertraline [26-29], fluoxetine [26,30,31], paroxetine [32-34], mirtazapine [34], citalopram [9,35], clomipramine [29,36,37] and nefazodone [38] have been studied. In addition, four RCT assessing the efficacy of the trazodone in ED were found [39-42]. AUA practice guidelines on the pharmacological management of PE were also available [43]. EAU guidelines on ejaculation disorders mention imipramine and desipramine for the symptomatic treatment of retrograde ejaculation [7]. In addition, two meta-analyses were retrieved, one discussing the efficacy of trazodone in ED [44] and another one the use of SSRI in PE [45].

Additional Searches

The subsequent search in Medline performed on the substance names of antidepressants applied in urology yielded a number of additional RCT on the pharmacological treatment of PE [46-55], (nocturnal and diurnal) enuresis [56-65], urinary urgency [66], overactive bladder [67], as well as treatment guidelines for enuresis in Taiwan [68].

The search in the Cochrane library provided one review paper on TCA and other antidepressants for the treatment of enuresis in children [69]; no Cochrane reviews were available related to SUI or ejaculation disorders. The EAU website provided guidelines on the pharmacological treatment of ejaculatory disorders [7].

Safety Information

All RCT studying the effect of duloxetine in SUI reported on the incidence of adverse events and

Table 1. Overview of RCT Addressing the Use of Amine Uptake Inhibitors in Urologic Disorders

Reference	Agent* /Dose	Type of study	Nr of pts	Safety data
SUI				
[13]	DUL 40mg bid	Double blind, PC	494	Nausea, dry mouth, constipation, fatigue, insomnia, dizziness, headache
[14]	DUL 40-60 mg bid	Double blind, PC	109	Nausea constipation, headache, dry mouth, fatigue, dizziness, insomnia, somnolence, vomiting One discontinuation due to worsened hypertension
[15]	DUL 40mg bid	Double blind, PC	458	Nausea, headache, insomnia, constipation, dry mouth, dizziness, fatigue
[16]	DUL 40mg bid	Double blind, PC	683	Nausea, fatigue, insomnia, dry mouth, constipation
[17]	DUL 20-80 mg/d	Double blind multi-centre, PC	24	Nausea, headache, dizziness, diarrhoea, hypertension, dysmenorrhoea
[18]	DUL 20-80mg/d	Double blind, PC	553	Nausea, fatigue, headache, dry mouth, constipation, insomnia, dizziness, somnolence, diarrhoea
Enuresis				
[20]	IMI 0.9-1.5 mg/kg/d OXY 15mg/d; IMI+OXY	Prospective, PC	77	No significant difference in side effects between pts on placebo and treatment
[21]	IMI 0.9mg/kg DESMO 30 µg/d	Multi-centre, open, cross-over	57	Few adverse effects with IMI: 1 pt with pallor, restlessness, cold extremities
[22]	IMI 25mg MIA 10mg	Multi-centre, double blind, PC	80	No adverse effects observed
[23]	AMI 25-50mg/d; DESMO 20µg/d; AMI/DESMO	Direct comparative	45	No significant side effects; 1 AMI patient with behavioural problems
[56]	IMI 1-2.5mg/kg/d	PC	18	Few adverse effects: 2 pts with dry mouth, 1 with transient, mild orthostatic changes
[57]	IMI up to 50 mg/d; behavioural therapy	no placebo	168	Not reported
[58]	IMI 25-50mg/d	Double blind, PC	27	Not reported
[59]	IMI 25-50mg/d, urine alarm; waiting list	Direct comparative	40	Not reported
[60]	IMI 25-50 mg/d	Double-blind, PC, cross-over	62	Not reported
[61]	IMI 10-25 mg/d, AMP random awakening, alarm	Double-blind, PC	60	IMI: 3 pts with lighter sleep, 2 pts with reduced appetite
[62]	IMI 50mg/d NOR 25mg	Double-blind, PC	298	IMI: 1 pt severe abdominal pain, 1 pt apathetic, belching, vomiting; NOR: 1 with rash, 2 pts toxic manifestations, 1 drowsy, 1 nauseous
[63]	IMI up to 50mg	Double blind, PC, cross-over	29	Transient dizziness in 1 pt
[64]	IMI 50-100mg/d	Double blind, PC, cross-over	28	No complications of the medication
[65]	AMI 25mg/d	Double blind, PC, cross-over	22	AMI: transient drowsiness and nausea in 1 pt
Urinary urgency				
[66]	IMI 1mg/kg	Double blind, PC	12	Nausea, fatigue, dizziness, flushing, headache, anxiety, stomach pain
Overactive bladder				
[24]	IMI/PROP 20/45 mg/d OXY 5mg/d, PT 5 mg/d	2 prospective cross-over studies	Study 1: 91; Study 2: 29	Dry mouth, constipation, visual disturbance, sleep disorders, weight gain, hoarseness Side effects most common with oxybutynin
[67]	FLU/NOR 1.5/30 mg/d	PC, cross-over	13	No adverse-event related drop outs, side effects not a problem
Interstitial cystitis				
[19]	AMI 25-100mg	Prospective	50	Anticholinergic effects in 92% of AMI pts (79% dry mouth)

*amine uptake inhibitor or comparator drug.

Abbreviations: pt/pts: patient/patients; IMI: imipramine; OXY: oxybutynin; PT: penthienate; PROP: propantheline; NOR: nortriptyline; FLU: fluphenazine; DUL: duloxetine; DESMO: desmopressin; AMI: amitriptyline; AMP: amphetamine; MIA: mianserin; PC: placebo-controlled; sign: significant.

Table 2. Overview of RCT Studying Antidepressant Drugs for the Treatment of PE and ED

Reference	Dose	Type of study	Nr of pts	Safety data
Trazodone for ED				
[39]	150 mg/d	Double blind, multi-centre, PC	69	Dizziness, sleepiness, headache, nausea; more common with TRA than placebo but not statistically significant
[40]	150 mg/d	PC	79	Mild sedation in 5 pts on TRA but no discontinuations
[41]	50 mg/d	Double blind, PC	51	TRA: 31% drowsiness, 19% fatigue, 1% dry mouth
[42]	200 mg/d	Double blind, PC	34	Not reported
Premature ejaculation				
Clomipramine				
[36]	25 mg AN		23	Not reported
[37]	25 mg AN	Double blind, PC, cross-over	34	Light-headedness, dry mouth, nausea, dizziness, visual disturbance, sleepiness
[52]	25 mg/d and 50 mg/d	Double blind, PC, cross-over	15	Dry mouth, constipation, feeling "different", dizziness, nausea, sleep disturbance, fatigue, hot flashes
[53]	25 mg/d and 50 mg/d	Double blind, PC	20	Mild nausea, transient drowsiness, constipation, transient erection difficulties
[54]	10-40 mg/d	Double blind cross over	20	Dry mouth, sweating, drowsiness
Paroxetine (SSRI)				
[29]	PAR 20 mg; CLO 25mg; SER 50 mg; SIL 50 mg	Comparative, no plac	31	Side effects mostly mild to moderate, no sign. diff between drugs: dry mouth, nausea, yawning, anorexia, sleepiness, drowsiness, yawning, nasal congestion
[32]	Study 1: 20 mg AN; Study 2: 10 mg/d - 20 mg AN	PC	Study 1: 26, Study 2: 42	Anejaculation, anorexia, gastro-intestinal complaints, reduced libido
[33]	20 mg/d and 40 mg/d	Double, no plac.	34	Yawning, perspiration, fatigue, nausea, dry mouth; side effects decreasing over time
[55]	20-40 mg/d	PC	17	Fatigue, frequent intense yawning
Fluoxetine				
[30]	20mg/d vs. 90 mg/wk	no plac.	80	Nausea, headache, insomnia; no difference between doses
[31]	20 mg/d	Double blind, PC	40	Loss of libido, fatigue, penile formication, somnambulism; anejaculation
[46]	20 mg/d and 20mg/d + lidocaine	no plac.	43	Nausea, headache, insomnia; no withdrawals due to side effects
[47]	20-40 mg/d	Double-blind, PC	17	Nausea, headache insomnia
Sertraline (SSRI)				
[26]	SER: 50 mg/d; FLUOX: 20-40 mg/d;	Comparative	57	Nausea, headache, insomnia; no difference in side effects between treatment groups; no withdrawals due to side effects
[27]	50 mg/d	PC	37	Headache, insomnia, dry mouth, diarrhoea; no withdrawals due to side effects
[28]	50 mg	PC	37	Drowsiness, anorexia, mild, transient gastrointestinal complaints; no withdrawals due to side effects
[38]	NEF: 400 mg/d, SER: 50 mg/d; PAR: 20 mg/d	PC	48	Slight decrease in penile rigidity and sexual desire in some pts of PAR and SER group; no sign. difference with placebo in non-sexual side effects
[48]	FLUOX: 20mg/d; FLUV: 100 mg/d; PAR: 20 mg/d; SER: 50 mg/d	PC	60	Slight decrease in penile rigidity and sexual desire in treatment groups; no sign. difference with plac. in non-sexual side effects
[49]	50-200 mg	PC	52	Diarrhoea, dry mouth, fatigue, anejaculation, ED; no withdrawals due to adverse events
Citalopram				
[9]	CIT: 20-60 mg/d	PC	26	Headache and nausea; no withdrawals due to side effects
[35]	CIT 20-60 mg/d vs. no therapy	No plac.	30	Gastrointestinal complaints, insomnia; no withdrawals due to side effects
[51]	CIT: 20mg/d; PAR: 20mg/d	Comparative, no plac.	30	PAR: slight decrease in sexual desire and penile rigidity in 3 pts; no sign. difference in nonsexual side effects

Abbreviations: pt/pts: patient/patients; CLO: clomipramine; plac: placebo; AN: as needed; PC: placebo-controlled; SER: sertraline, PAR: paroxetine, FLU: fluoxetine, FLUV: fluvoxamine; NEF: nefazodone; TRAZ: trazodone; CIT: citalopram; SIL: sildenafil.

discontinuation rates. Most RCT dealing with TCA in nocturnal enuresis and SSRI in PE provided safety data, but the information was often not systematically reported, especially in the older studies. No RCT were found assessing the safety profile of TCA in the treatment of retrograde ejaculation, but one non-randomised clinical trial was found to report on adverse effects [70].

The consulted FDA website contained data on safety of duloxetine, citalopram, fluoxetine, paroxetine, and sertraline. The labels of imipramine, amitriptyline or nortriptyline were not available, but the PDR website contained safety information for these TCA [71].

It is to be noted that all antidepressants - including TCA - carry a recently issued warning from the FDA on the increased risk of suicidal behaviour when used in paediatric patients.

DISCUSSION

The searches revealed more data on the SNRI duloxetine in SUI than on other amine uptake inhibitors used in the treatment of PE, retrograde ejaculation and enuresis. This is probably explained by the fact that duloxetine has been subject to a full development program quite recently in order to obtain registration for the treatment of SUI, while this has not always been the case for the other applications of antidepressants in urology.

ON-LABEL USE OF AMINE UPTAKE INHIBITORS IN UROLOGY

The SNRI *Duloxetine* in SUI

Urinary incontinence is a common and highly bothersome condition, occurring in about 35% of adult women [72,73]. SUI is defined as the complaint of involuntary leakage on effort or exertion, or on sneezing or coughing [74]. Stress symptoms are the most common manifestation of urinary incontinence, with 37-42% of incontinent women reporting pure SUI, while 33-46% report mixed stress and urge urinary incontinence symptoms [72,73]. SUI may be due to a hypermobile bladder neck and/or urethra, urethral striated sphincter (rhabdosphincter) deficiency, or a weak or injured pelvic floor [75]. To date, SUI has been treated with lifestyle interventions such as quitting smoking, fluid management and weight loss complemented with pelvic floor muscle training or, in more severe cases, vaginal devices or surgery [76]. Until recently, no universally approved pharmacological treatment was available, although several drugs including estrogens, α -adrenergic receptor agonists, β -adrenergic receptor antagonists, TCA, and anticholinergic agents have been tried off-label with limited, if any, success [6]. The SNRI duloxetine is the first pharmacological agent that is approved by the EMEA for the treatment of SUI [77]. SNRI have also been incorporated in the revised guidelines for the pharmacological treatment of SUI, elaborated by the 3rd International Consultation on Incontinence (Monaco 2004), with a grade A recommendation, which comprises the highest level of evidence (i.e. high quality RCT, meta-analysis or systematic reviews of RCT) [12].

The rationale for using an SNRI for treating SUI is based on the finding that 5-HT and NA are implicated in the

central control of lower urinary tract function. Sudden increases in abdominal pressure upon physical efforts (e.g. coughing) require an adequate "guarding reflex" in order to prevent the loss of urine during physical efforts, as is the case in SUI. This guarding reflex is provided through an increased contraction of the striated muscle of the distal urethra, which is mediated by acetylcholine released from the somatic pudendal nerve and the sacral nerve fibres acting on nicotinic acetylcholine receptors. The cell bodies of this pudendal nerve possess a high density of 5-HT and NA terminals and receptors [78]. The stimulation of these receptors results in an increased guarding reflex, which prevents urine leakage. These mechanisms are under central control, with the main descending neurotransmitter being glutamate, which acts as the on/off switch for micturition. The neurotransmitters 5-HT and NA are assumed to facilitate the activity induced by glutamate, and elicit a stronger contraction of the urethral rhabdosphincter during the urine storage phase [79]. The withdrawal of glutamate results in voiding, irrespective of the presence of 5-HT or NA. Hence, the mode of action of duloxetine is presumably based on the prolongation of the activity of 5-HT and NA, facilitating storage and guarding reflex, while having no effect on the micturition phase.

The results of several RCT have yielded convincing evidence for the efficacy of duloxetine in women with moderate and severe SUI in reducing incontinence episode frequency [13-15]. The mean improvement on the incontinence in quality of life, measured with an incontinence specific tool (the Incontinence Quality of Life Questionnaire) was significantly greater in the duloxetine patients than in those treated with placebo [13-16].

TCA in Nocturnal Enuresis

Nocturnal enuresis has been defined by the International Continence Society as the complaint of loss of urine occurring during sleep [74]. It is normal voiding that happens at an inappropriate and socially unacceptable time and place [80]. Children over five years of age who still wet in bed are considered enuretic. It is a common problem in children, with an estimated 15% of children over five affected, and it is more prevalent in boys than in girls [22]. While the bell and pad alarm system provides higher success and lower relapse rates than pharmacological treatment, drugs may be useful to cover short periods when dryness is essential such as school trips or holidays [22]. Pharmacological treatment of nocturnal enuresis consists mainly of a synthetic vasopressin analogue, desmopressin, or the TCA imipramine [80]. Imipramine has been in use for decades for the treatment of nocturnal enuresis, the oldest clinical trials that were found in Medline dating back to the '60s [61-64]. Its mode of action in enuresis is not completely understood. It has been suggested that the anticholinergic effects of the drug result in a decrease in bladder contraction leading to increased bladder filling and improved functional bladder capacity [80]. Imipramine is generally reported to be more effective than placebo, with an average reduction of wet nights around 50% [81].

Treatment guidelines of enuresis in Taiwan recommend imipramine as one of the treatment options for children from 5 or 6 years old, but warn about the potential toxicity of the

drug [68]. The EAU guidelines on the treatment of enuresis recommend the use of desmopressin and not imipramine as pharmacological treatment for nocturnal enuresis in children, but TCA are recommended as pharmacotherapy for daytime enuresis in children with attention disorders [82]. Nevertheless, imipramine is registered in several European countries (e.g. the Netherlands and Germany) for the treatment of nocturnal enuresis in children.

OFF-LABEL USE OF AMINE UPTAKE INHIBITORS IN UROLOGY

SSRI and TCA in Premature Ejaculation

A universally accepted definition of PE, sometimes also referred to as rapid ejaculation, has yet to be established, but AUA guidelines on the treatment of the disorder define it as "ejaculation that occurs sooner than desired, either before or shortly after penetration, causing distress to either one or both partners" [43]. PE is the most common ejaculatory disorder, with a prevalence estimated to be around 29%, ranging from 1% to 75% depending on the target population and the study criteria [83]. Although PE does not impair fertility provided intravaginal ejaculation occurs, it is often highly bothersome for those affected and/or their partners.

The control of ejaculation is apparently governed by interacting levels of the nervous system: (1) the modulator influence from the supraspinal level, (2) interaction at the spinal cord level and (3) sensory input determining the amplitude of the sacral reflex (infraspinal level) [31]. 5-HT acting at the supraspinal level has an inhibitory effect on sexual function, while dopamine is in general stimulatory, as has been shown in animal studies [84,85]. Any shift in this dopamine-5-HT balance can induce sexual effects. Hence, any agent that increases the availability of central 5-HT has the potential to reduce sexual excitement and to have a beneficial effect on PE. This is corroborated by the observation that the use of amine uptake inhibitors, especially the ones influencing 5-HT availability, is associated with sexual side effects including delaying ejaculation or increasing ejaculation latency time and inhibiting orgasm in men. This has lead researchers to investigate the potential of antidepressive agents as a therapy for PE.

The RCT show the TCA clomipramine to increase ejaculatory latency time by several minutes [36,37,52-54]. Likewise, the SSRI sertraline, fluoxetine, paroxetine and citalopram were proven to be more effective in treating PE than placebo [9,26-35]. In contrast, nefazodone, a combined 5-HT/NA uptake inhibitor and 5-HT₂ antagonist, was not effective in delaying ejaculation latencies [38]. These findings are consistent with observations in psychiatric patients where antidepressants (with the exceptions of nefazodone and bupropion) have routinely been associated with adverse effects on sexual function [86].

Clomipramine, fluoxetine, sertraline and paroxetine are recommended as a medical therapy for the treatment of PE according to the guidelines of the AUA [43,87], but none of these agents are approved by the FDA for this specific indication [43]. Guidelines on the treatment of ejaculatory disorders from the EAU do not incorporate any specific

pharmacological therapy for PE [7], and none of these agents has an EMEA approval for the treatment of PE.

TCA in Retrograde Ejaculation

The EAU defines retrograde ejaculation as "the total absence of antegrade ejaculation because semen passes backwards through the bladder neck into the bladder" [7]. Patients experience a normal or decreased orgasmic sensation, except in paraplegia. The aetiology of retrograde ejaculation includes neural injury, urethral obstruction and bladder neck incompetence. In addition, retrograde ejaculation may be a side effect of various drugs [7,88]. Retrograde ejaculation can be treated with drugs that exert an NA reuptake inhibition effect such as TCA (imipramine, desipramine) [88]. Alternatively, adrenergic drugs such as ephedrine may also prove efficacious [88].

EAU guidelines on ejaculatory disorders recommend the TCA imipramine (25-75 mg three times daily) or desipramine (50 mg every second day) for the symptomatic treatment of this disorder [7].

Other Applications of Amine Uptake Inhibitors in the Urological Setting

The efficacy of trazodone has been assessed for the treatment of ED. Although several of the RCT that were retrieved in the searches yielded evidence that trazodone was somewhat effective against ED, this was not significant compared to placebo [39-42]. A recent meta-analysis suggested nevertheless that trazodone may be effective against ED in higher doses [44].

Amitriptyline has been reported to be significantly more effective against interstitial cystitis than placebo [19]. Amitriptyline is mentioned as a possible pharmacological treatment for interstitial cystitis in the EAU guidelines [89].

Combination therapy of fluphenazine and nortriptyline has been reported to be effective against unstable bladder [67]. Another study reported that a combination of imipramine and propantheline improved urinary symptoms and urodynamic changes associated with unstable bladder to a similar extent as the antimuscarinic agent oxybutynin [24].

Safety of Amine Uptake Inhibitors in the Urological Setting in Comparison to Psychiatric Populations

SNRI (Duloxetine) in SUI

The reported side effects in duloxetine-treated SUI patients are summarised in Table 1. These adverse events are usually mild to moderate [13-18], and duloxetine's safety profile in the elderly (≥ 65 y) is comparable to that in younger subjects [17]. Nausea is the most frequently reported adverse event, and the most common adverse event leading to treatment discontinuation: 13-46% of the duloxetine-treated patients reported nausea in the RCT, and 3-6% of the patients discontinued treatment because of nausea relative to respectively 2-13 % and 0-1% of patients receiving placebo [13-16,18]. However, nausea is mild to moderate in the majority of cases, and usually resolves within 1 to 4 weeks of treatment. The majority of SUI patients reporting nausea continued the studies, which indicates that this side effect is deemed acceptable by most patients. In addition, a recent dose-escalating study showed

that women treated with duloxetine for SUI who started on lower doses (20 mg b.i.d. or 40 mg q.d.) during two weeks before escalating to the recommended efficacious dose of 40 mg b.i.d. experienced less nausea than those receiving a dose of 40 mg b.i.d. right from the start (respectively 17%, 25% and 29% of patients reporting nausea versus 6% of placebo-treated women) [90]. The discontinuation rate in the group subject to dose escalating (8%) was also lower than in the groups who started on 40 mg q.d. and 40 mg b.i.d. (respectively 12% and 16%), and was comparable to placebo (6%).

Other frequently reported adverse events include fatigue (10-15%), insomnia (13-14%), dry mouth (12-19%), constipation (10-14%), dizziness (8-12%), and headache (7-15%) [76]. In line with the data on nausea, a reduction in the prevalence of dizziness was observed in women who took escalating doses of duloxetine: among those patients who took 20 mg b.i.d. before dose escalating, 3% reported dizziness. In contrast, of the women who took 40 mg q.d. or 40 mg b.i.d., respectively 8% and 10% experienced dizziness during duloxetine treatment [90]. In the placebo group 0.8% of the patients reported this side effect.

A significant increase in mean heart rate was reported compared to placebo, but the less than 3 beats per minute increase with duloxetine remained within the normal range, with no clinical relevance [13,15]. No arrhythmogenic tendencies were observed with duloxetine [13,15]. Serious adverse events, cardiovascular events and laboratory abnormalities were rare and not significantly more common in the duloxetine group than in the placebo group [13,16]. No statistically significant differences in the mean change of systolic or diastolic blood pressure between the drug and the placebo group were recorded in two of the studies [13,15]. Another study reported hypertension in 13% of the subjects (3/24), but all blood pressure elevations were transient [17]. Worsening hypertension resulted in treatment discontinuation in 2 out of 55 duloxetine treated patients in one of the trials in women with severe SUI awaiting surgery [14]. However, in the same trial the rates of serious adverse events, cardiovascular events or laboratory abnormalities were not significantly different to placebo [14]. However, the FDA safety data on duloxetine mentions possible increases in blood pressure averaging 2 mm Hg (systolic) and 0.5 mm Hg (diastolic) [91]. It is recommended to monitor blood pressure in patients with known hypertension and/or other cardiac disease when duloxetine is administered [92].

Viktrup *et al.* investigated the risk of mania or hypomania in women with SUI treated with duloxetine and found that the drug did not induce mania or hypomania in this patient group. In this population few women had a history of depression or bipolar disorder and those on antidepressants were excluded from the study [93].

Given that the mode of action of duloxetine is thought to be related to enhanced contraction of the rhabdosphincter in the lower urinary tract, a theoretical possibility exists that duloxetine may increase the risk of urinary retention [94]. However, a pooled analysis of clinical trials assessing the relationship between duloxetine and obstructive voiding symptoms in patients with depressive disorder or SUI showed that duloxetine does not induce urinary retention

[94]. This can probably be explained by the purely modulating effect of 5-HT and NA in the control of the lower urinary tract [94].

Inhibition of 5-HT reuptake may also result in sexual side effects, due to the effect of 5-HT on sexual function. However, no sexual side effects have been reported in any of the SUI trials with duloxetine [13-18]. On the other hand, studies with duloxetine in depressed patients have reported adverse effects on sexual desire and orgasmic function [95,96].

To conclude, duloxetine is generally well tolerated in the urological setting. Dose escalating provides a means for reducing the most common adverse effects, in particular nausea and dizziness, and leads to a decrease in withdrawals due to adverse events. In addition, proper patient counselling about the possibility of transient nausea would most likely lead to increased compliance and decreased adverse event-related dropouts.

SNRI Safety Data in Psychiatric Patients

Adverse events associated with the use of SNRI in psychiatric patients (duloxetine and venlafaxine) are comparable to those reported for duloxetine in the SUI trials. This is not unexpected as the daily doses in SUI and MDD applied are in the same range; the recommended daily dose in SUI amounts to 40 mg b.i.d. while in MDD the administered dose tends to vary from 60 to 120 mg daily, although 40 mg/d has been prescribed as well [97,98].

A pooled analysis of placebo- and active comparator-controlled trials of duloxetine in patients treated for MDD showed nausea to be a common side-effect: it was reported in up to 20% of patients on duloxetine in doses from 40 mg to 120 mg daily, versus 7% for the patients on placebo [99]. Median time to onset of nausea was 1 day, and the median duration of nausea amounted to 7 days. As reported for SUI patients, nausea tended to be mild (53% of patients) or moderate (41%). Head-to-head studies comparing duloxetine with the SSRI paroxetine and fluoxetine revealed no significant difference in the prevalence rates of nausea [99]. After one week, the incidence of nausea was similar in placebo and treatment groups. In continuing duloxetine therapy the incidence of treatment-emergent nausea remained similar to placebo after six months. The occurrence of nausea is probably due to the effect of 5-HT, 90% of which is present in the gastrointestinal tract; nausea and vomiting probably result from the effects of 5-HT on peripheral and central 5-HT receptors. Hence, any drug increasing 5-HT levels is likely to induce nausea [99]. It has been suggested that the decline in nausea during long-term treatment may be due to a gradual desensitisation of 5-HT₃ receptors [99]. From the data on longer term duloxetine treatment in psychiatric patients, it may be hypothesised that nausea will probably disappear during sustained treatment of SUI in most patients, but this hypothesis awaits confirmation in trials assessing the long-term effects of duloxetine in SUI.

Cardiovascular effects of SNRI (duloxetine, venlafaxine) in psychiatric patients comprise mainly slightly increased heart rate and transient increases in blood pressure [100-102]. Venlafaxine induces dose-dependent increases in supine diastolic blood pressure, but the incidence of elevated blood pressure is only statistically and clinically significant

at high doses (>300 mg/d). Venlafaxine does not adversely affect blood pressure control in patients with pre-existing hypertension or elevated baseline values [101]. Abrupt discontinuation of duloxetine treatment was associated with small increases in heart rate [102]. A pooled analysis of 8 clinical trials in depressed patients revealed that duloxetine increased the heart rate compared to placebo (+1.6 vs. -0.6 beats per minute) and systolic blood pressure (+1.0 vs. -1.2 mm Hg). The difference for diastolic blood pressure was not statistically significant between duloxetine and placebo (respectively +1.1 vs. +0.3) [100]. This is congruent with the slight, but not clinically relevant, increase in blood pressure and/or heart rate that were shown in some of the RCT assessing the safety of duloxetine in SUI [13,14,17]. The FDA safety data on duloxetine confirms that heart rate may increase with on average 2 beats per minute, besides the possible increases in blood pressure that have been described earlier [91]. Mania or hypomania was reported in 0.1% of the patients, which was a similar percentage as placebo [91]. Although the drug has not been systematically investigated in patients with cardiac disease, electrocardiograms taken from patients on duloxetine did not reveal any clinically relevant abnormalities. It is important to note, however, that there were no differences between duloxetine and placebo in the incidence of sustained (≥ 3 consecutive visits) systolic or diastolic blood pressure elevation [100]. In addition, head-to-head comparisons of duloxetine with the SSRI fluoxetine and paroxetine showed no significant differences in mean changes of blood pressure between drugs. The authors concluded that the cardiovascular effects of duloxetine were comparable with other medications that are considered as a first line therapy in the treatment of depression [100].

Sexual side effects of SNRI include mainly decreased libido, ED, ejaculatory disorders and abnormal orgasm [91]. This is in line with the well-known effects of 5-HT reuptake inhibition on sexual function. That no sexual side effects have been reported in any of the SUI trials with duloxetine is probably explained by the fact that these effects have mainly been reported in male patients treated for MDD, and only in a small proportion of the patients (3-6%). Female duloxetine-treated patients may be affected by abnormal orgasm or decreased libido, but the prevalence is even lower than in men (1-2% of patients) [91].

Safety of TCA in Retrograde Ejaculation and Nocturnal Enuresis

Ochsenkühn *et al.* carried out a non-randomised clinical trial on the effect of imipramine (25-50 mg daily) on retrograde ejaculation caused by retroperitoneal surgery and reported that half of the patients experienced minor degrees of dizziness, nausea, weakness and increased sweating, while no major side effects were reported [70].

Safety assessments from the RCT dealing with nocturnal enuresis report imipramine to be generally well tolerated in paediatric patients, but not all studies have reported on side effects (Table 1). However, a recent data pooling of 480 enuretic patients showed imipramine to be associated with a fairly high prevalence of gastro-intestinal and neurological side effects [81]. PDR data mention nervousness, sleep disorders, tiredness, stomach and intestinal problems as the most common side effects in children being treated for

bedwetting [71]. Less frequent side effects in children comprise anxiety, collapse, constipation, convulsions, emotional instability and fainting [71].

Safety Data of TCA in Psychiatric Patients

TCA are not only 5-HT and NA reuptake inhibitors but also antagonists at muscarinic acetylcholine, α_1 -adrenergic and histamine receptors, which may lead to numerous side effects [1]. Due to their antimuscarinic effect TCA are associated with constipation, blurred vision, dry mouth and drowsiness. Their antihistaminic effect leads to weight gain and drowsiness, while the blockade of α_1 -adrenergic receptors may induce hypotension, dizziness, and decreased blood pressure [1].

While most side effects of TCA in the psychiatric setting are not life-threatening, their cardiovascular toxicity can be lethal, especially in overdose [103]. Cases of serious TCA overdose have often been associated with conduction defects and arrhythmias. Especially patients with pre-existing conduction disease are at risk, even at therapeutic doses [103]. Apparently, few differences in cardiotoxicity exist between the various types of TCA, and the occurrence of serious cardiovascular complications seems to be more a function of the patients pre-existing cardiac disease [103]. The most common cardiovascular side effects associated with TCA, however, is orthostatic hypotension. Nortriptyline has been shown to cause less postural hypotension than other TCA [103]. Imipramine causes a decreased vagal function with a relative increase in sympathetic responsiveness in children, which may be related to its cardiotoxicity [104]. Hence, considering the cardiotoxicity of TCA, their use in a relatively benign condition such as childhood enuresis can hardly be recommended.

PDR data mention a large number of side effects including cardiac symptoms, urinary symptoms, sexual dysfunction, dizziness, drowsiness, dry mouth, headache, gastro-intestinal complaints, swelling, weight gain or loss, associated with the use of TCA [71,105].

Safety of SSRI and TCA in PE

Side effects associated with the use of the various amine uptake inhibitors in PE are presented in Table 2. Most frequently reported side effects associated with clomipramine in PE comprise dry mouth, constipation, dizziness, nausea and sleep disturbance; adverse event rates appear to be dose-related [52].

Adverse effects related to the use of SSRI in PE include nausea, headache, dry mouth, insomnia, drowsiness, anejaculation and reduced libido [9,26,28,31,32,46,47,50]. However, these occurred relatively rarely, considering that several studies reported no difference in prevalence of non-sexual side effects between the treatment and the placebo group [34,48,51]. Moreover, the reported adverse effects tend to be mild and seem acceptable to most patients, considering that most RCT report few if any discontinuations due to adverse events [26-28,31,50].

Safety of SSRI in the Psychiatric Setting

Congruent with the safety data in PE and with the physiological effects of 5-HT reuptake inhibition, nausea is one of the most common side effects of SSRI applied in

psychiatric patients [106]. Around 12-17% of MDD patients treated with SSRI are affected by nausea [99,107]. In general, gastrointestinal side effects including peptic ulcers are more common with SSRI than with TCA, especially when non-steroidal anti-inflammatory drugs are used concomitantly [108].

Other side effects include sleep disturbance, fatigue, anxiety, nervousness, weight gain or loss, dermatological reactions, cognitive and psychomotor impairment [1,106].

Contrary to TCA, SSRI are not lethal in overdose. SSRI have minimal cardiovascular side effects in patients without cardiac disease. The cardiovascular side effects of SSRI in patients with cardiac disease have been less thoroughly evaluated, but head-to-head comparisons with TCA in this patient group show SSRI to induce less cardiovascular effects [109]. SSRI are apparently less associated with hypotension or conduction abnormalities than TCA, but may induce bradycardia [109]. In patients with existing cardiac disease, SSRI are also associated with less cardiovascular effects than TCA [110], but statistically significant decreases in heart rate and increases in supine systolic blood pressure have been reported [109].

Sexual dysfunction, especially ejaculatory delay, is a common adverse class effect associated with the use of all SSRI in psychiatric patients [111]. Whereas this may be considerably bothersome to the psychiatric patient, it provides the rationale for the drug to be applied in PE. The severity of the effect on ejaculation varies across drugs, however. Paroxetine is associated with more sexual side effects than sertraline and fluoxetine [112]. This is confirmed by the results of Waldinger *et al.*, who reported paroxetine to be more effective in the treatment of PE than other SSRI [38,48,51].

FDA safety information on fluoxetine, citalopram, paroxetine and sertraline confirms nausea as the most common adverse event. Other side effects include asthenia, dry mouth, diarrhoea, anorexia, anxiety, somnolence, insomnia and nervousness [113-115]. Sexual side effects include decreased libido, orgasmic dysfunction and priapism. Hypertension, hypotension, haemorrhage and palpitations are reported as the most common cardiovascular side effects. Most SSRI-related adverse events are mild to moderate in severity and the gastrointestinal events tend to diminish over time [106]. In addition, SSRI may affect mood in psychiatric patients [106], but no such effects were reported in the RCT on PE.

Although the side effects of amine uptake inhibitors in other settings than depression have been assessed to a lesser extent, the adverse event profiles of antidepressants in PE appear to be similar to those reported in patients treated for depression described above [87].

Considering that drug doses employed in the treatment of PE are often lower than in clinical depression, especially when administered on an as-needed basis prior to intercourse, it is not unlikely that the frequency as well as the severity of adverse events of SSRI in PE will be less. For example, clomipramine is effective for PE in doses of 25 mg/d, while it is often prescribed in doses of 100-150 mg/d in MDD. Fluoxetine may be effective in PE at a dose of 5-10 mg daily, while the recommended dose in adults with MDD

is 20 mg/d [113]. The low prevalence of side effects associated with amine uptake inhibitors in PE is confirmed by the observation of few or no differences in non-sexual side effects in several of the RCT between treatment and placebo groups [34,48,51], and it is also reflected in the low discontinuation rates in PE patients treated with SSRI.

Adverse Effects Related to Discontinuation of Antidepressants

Abrupt discontinuation of antidepressant therapy can be associated with the occurrence of adverse events. These symptoms may be somatic (e.g., dizziness and light-headedness; nausea and vomiting; fatigue, lethargy, myalgia, chills, and other flu-like symptoms; sensory and sleep disturbances) or psychological (anxiety and/or agitation, crying spells, irritability) [116]. They occur with both SSRIs and TCAs, and their occurrence is inversely related to the plasma half-life of the antidepressant (including applicable active metabolites) [117]. Most reactions are mild and short-lived and require no treatment other than patient reassurance. Nevertheless, antidepressant-withdrawal hypomania or mania may occur rarely upon abrupt or tapered withdrawal or dose reduction [118]. Severe cases of antidepressant discontinuation syndrome can be treated symptomatically or the antidepressant can be reinstated before being gradually withdrawn; reinstatement usually leads to symptom resolution within 24 hours [117]. Dose tapering rather than abrupt discontinuation is recommended when the decision of treatment withdrawal has been made [116].

Adverse events which are significantly more common in depressed patients who discontinued abruptly from duloxetine than in those withdrawing from placebo include dizziness, nausea, headache, paraesthesia, vomiting, irritability and nightmares [91]. The EMEA product information sheet on duloxetine recommends dose tapering from 40 mg twice daily to 20 mg twice daily for 2 weeks in order to decrease the risk of possible discontinuation symptoms [77]. The study of Bump *et al.* reported that dose tapering of duloxetine in SUI patients had no significant effect on reducing the overall incidence of adverse events, but that tapering from the recommended 40 mg twice daily to 40 mg once daily for two weeks might reduce the risk of the most common discontinuation adverse event, dizziness [90].

Suicide and Self Harm Associated with the Use of Antidepressants

Weak evidence for an increased risk of self harm has been found with use of SSRI [119]. Others have reported venlafaxine, trazodone and mirtazapine, but not SSRI to be associated with increased risk of self harm in the case of overdose [120]. No such data is available for duloxetine.

Following a series of case reports in the '90s, it has been suggested that antidepressants may increase the risk of suicidal behaviour [121]. Recent reviews found no evidence for increased risk of suicide associated with the use of SSRI in patients treated with these drugs for depression or for other reasons [121]. Others observed a positive correlation with TCA prescription rates and suicide, whereas lower suicides rates were found for users of non-TCA antidepressants including SSRI and SNRI [122]. It has also

been hypothesised that depressed patients subject to pharmacotherapy who experience adverse events are prone to develop suicidal behaviour, but this could not be substantiated either [123]. However, in a recently issued statement, the FDA warns of increased risk of suicidal thinking and behaviour in paediatric patients treated with antidepressants, which can be expected in about 1 out of 50 treated paediatric patients [113]. The FDA recommends that all patients on antidepressants should be monitored closely for clinical worsening and suicidality, especially during the first months of therapy, as well as when the dose is modified. This warning has been issued for all classes of antidepressants [124]. Likewise, the European regulatory authorities have issued similar warnings regarding the use of SSRI and SNRI in children [125].

CONCLUSIONS

It is clear that amine uptake inhibitors fulfil an important role in the treatment of various urological and sexual disorders that may not be life-threatening, but which diminish the quality of life of those affected. Main domains are SUI and PE, and nocturnal enuresis. AUA guidelines recommend several SSRI and the TCA clomipramine as off-label treatment for PE. Nocturnal enuresis should preferably not be treated with the TCA imipramine as a first-line therapy because of its associated side effects.

Our literature search, focussing on the outcomes in RCTs, suggests that duloxetine in SUI and clomipramine and SSRI in PE are effective, safe and generally well tolerated. Nausea, a frequently reported adverse event associated with the use of SNRI and SSRI, is usually mild to moderate and transient. Comparing safety data from the urologic setting with those from psychiatric populations, for which long-term safety data is available on large numbers of patients, shows that adverse events are similar in both settings, qualitatively as well as quantitatively. Strategies for minimising patient discomfort include slowly escalating doses and proper counselling with regard to the possibility of the (transient) side effects.

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