



Neuro-urology

Effective Treatment of Neurogenic Detrusor Dysfunction by Combined High-Dosed Antimuscarinics without Increased Side-Effects

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Abstract

Objectives: Patients with neurogenic bladder dysfunction demonstrate an insufficient treatment outcome under dosage-escalated monotherapy. With the objectives of continence and normalised bladder pressure, safe and tolerable non-invasive treatment alternatives were evaluated by using combined antimuscarinics.

Methods: Twenty-seven patients who were previously registered in a doubled antimuscarinics study were enrolled in this study. The patients demonstrated urodynamic-proven neurogenic bladder dysfunction with incontinence, reduced bladder capacity, and increased intravesical pressure, resulting from spinal cord injury ($n = 21$); spinal cord dysplasia (myelomeningocele; $n = 3$); multiple sclerosis ($n = 2$), and viral encephalomyelitis ($n = 1$). On the basis of the initial study treatment, they were allocated into three groups and treated with two antimuscarinics. Before enrolment, at 4 wk, and at 6 mo, patients underwent urodynamics and recorded bladder diaries, including side-effects. **Results:** In all three groups, significant changes were noted at the 4-wk follow-up. Incontinence events decreased from an average of 7 to 1 event per day. The average median bladder capacity (180–393 ml) and reflex volume (125–335 ml) increased; detrusor compliance also improved (average, 15–33 ml/cm H₂O). Seven patients reported side-effects; two discontinued the successful treatment. Two other patients did not reach satisfactory amelioration of the detrusor dysfunction.

Conclusion: With combined high-dosage antimuscarinic medications, 85% of the patients who previously demonstrated unsatisfactory outcome with dosage-escalated monotherapy were treated successfully. The appearance of side-effects was comparable to that of normal-dosed antimuscarinics. Further studies are required to investigate the long-term pharmacological and physiological background of our findings.

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1. Introduction

The development of neurogenic bladder dysfunction is often one of the clinical symptoms that develop after a spinal cord injury (SCI). Patients suffering from multiple sclerosis or other spinal cord diseases such as neuroectodermal dysplasia (e.g., myelomeningoceles) frequently develop overactive bladder dysfunction. The patients' primary problem is involuntary loss of urine triggered by sudden bladder contractions.

In SCI patients, detrusor-sphincter-dyssynergia starts after the period of bladder acontractility and can carry a high risk of complications; even life expectancy can be affected. In contrast, multiple sclerosis patients, for example, develop overactive spontaneous bladder contractions. It is primarily uncontrollable, recurring incontinence that causes the patients' stressful situation, resulting in a distinct reduction in quality of life.

The goal of urological therapy of neurogenic bladder dysfunction is continence and normalised pressure in the lower urinary tract [1]. Continence, combined with frequent, clean intermittent catheterisation, helps to significantly reduce urological infections, disruptions of the upper urinary tract, and patient dissatisfaction [2,3]. Most patients receive an oral antimuscarinic treatment [4]. Long-lasting experience and multiple clinical studies with antimuscarinic drugs have demonstrated their effectiveness in treating neurogenic bladder dysfunction. Tolterodine, oxybutynin, and trosipium are typical antimuscarinic agents that are well tolerated, despite published side-effects such as dry mouth, blurred vision, dry skin, and constipation.

However, for some patients, these antimuscarinic drugs often fall short because of these side-effects or insufficient effect with continuing incontinence. Madersbacher et al [5] described that almost 30% of their treated patients suffered from persistent symptoms of detrusor overactivity. Madersbacher, along with van Kerrebroeck et al [6,7] and Appell [8], have reported increased effectiveness with increased quantities of antimuscarinic drugs.

In light of these earlier studies, we previously reported an improved therapeutic strategy with dosage-doubling of these antimuscarinic drugs [9] in our clinic. Interestingly, we noted that the side-effects did not occur more often or more severely than at the recommended dosage. In fact, some patients treated with the increased levels of antimuscarinics still continued to suffer from incontinence caused by autonomous bladder contractions from DSD.

On the basis of the initial study results [9], we hypothesised that an additional antimuscarinic drug could be combined with the existing doubled medication to improve continence, bladder capacity, and intravesical pressure; the results of this treatment have not been published previously.

2. Methods

2.1. Patient enrollment and evaluation

Patients ($n = 27$) from the previous double-dosage antimuscarinic monotherapy whose initial symptoms did not resolve and who experienced mild or no side-effects were enrolled. The study was approved by the local ethics committee. The enrolled patients demonstrated (both in the initial study and present study) urodynamic-proven neurogenic bladder dysfunction with incontinence, reduced bladder capacity, and increased intravesical pressure, resulting from SCI in the chronic phase ($n = 21$ [15 with tetraplegia and 6 with paraplegia], spinal cord dysplasia [myelomeningocele; $n = 3$], multiple sclerosis [$n = 2$], and viral encephalomyelitis [$n = 1$]) (Table 1). All patients practiced clean intermittent catheterisation or were catheterised by a second person.

The study group consisted of 21 male and 6 female patients with an average age of 35.7 yr (range 18–62 yr). Their preliminary status in the present study was evaluated by using the previous study's [9] urodynamic results and bladder diaries. Inclusion criteria for participation were age (minimum 18 yr) and the development of neurogenic bladder dysfunction verified by urodynamic results at the time of enrolment to establish a baseline. All participants provided informed consent before enrolment in the study.

On the basis of the previous doubled monotherapy study [9], the patients in the present study were allocated into three pre-determined treatment groups; they maintained their doubled dosage from the initial study while being introduced to the second antimuscarinic drug at the lowest possible dosage to reduce any risk of adverse events. It was decided that the study would maintain the three drugs from the initial study, because these drugs were well tolerated by the patients. Patients were closely monitored for 4 wk under a consistent drug setting for possible side-effects. The dosage of the second drug was increased as needed according to patient feedback and a review of their diaries, while ensuring that the combination was uneventfully tolerated and urodynamic results continued to be positive (Table 2).

Table 1 – Patient characteristics

Patients (n)	27
Male (n)	21
Female (n)	6
Average age (yr)	35.7
Range of age (yr)	18–62
Spinal cord injury (n)	21
Spinal cord dysplasia (n)	3
Multiple sclerosis (n)	2
Viral meningoencephalitis (n)	1

Table 2 – Resultant administered dosage of antimuscarinics at 4-wk follow-up

Consecutive patient no.	Group A		Group B		Group C	
	First tolterodine (mg)	Second oxybutynin (mg)	First trospium (mg)	Second tolterodine	First oxybutynin (mg)	Second trospium (mg)
First study						
Recommended dosage	4		45		15	
Doubled dosage	8		90		30	
Second study						
1	8	15	90	4	30	45
2	8	20	90	8	30	60
3	8	30	90	4	30	60
4	8	25	90	6	30	45
5	8	15	90	6	30	45
6	8	15	90	8	30	75
7	8	20	90	4	30	90
8	8	25	90	4	30	45
9			90	6		
10			90	4		
11			90	8		

Grey shading = drop outs due to unsatisfactory outcome (both at the combined doubled dosage).
Orange shading = drop outs due to side-effects.

2.2. Urodynamic studies

Before starting the study, the urodynamic examination and the urine status were verified to exclude measurement failures based on urinary infection. If a urinary infection was found, the patient received an antibiotic treatment and was re-evaluated 1 wk later. The urodynamic examination confirmed the diagnosis of neurogenic bladder dysfunction noted in the first study.

A SEDIA NT (Sedia, Givisiez, Switzerland) with a double microtip catheter (UROBAR, 9 Ch; Raumedic AG, Helmbrechts,

Germany) was used to perform the video-urodynamics; the following data were recorded and analysed: maximal bladder capacity, reflex volume of the bladder, maximum detrusor pressure, and detrusor compliance.

The bladder was filled with 37 °C saline via the transurethral microtip catheter at a filling rate of 20 ml/min. For the video-urodynamic examination, contrast medium (Ultravist; Bayer HealthCare Pharmaceuticals, Berlin, Germany) was mixed with the saline filling solution. For calculation of intravesical pressure, a rectal balloon catheter was inserted into the rectum to register intra-abdominal pressure. The urodynamic unit also recorded registration of pelvic floor muscle activity by electromyogram with adhesive electrodes attached to the perineum.

Before enrolment and at the 1-mo and 6-mo (final) follow-up under the effective or tolerated antimuscarinic dosage, the patients underwent a urodynamic examination. Urodynamic parameters for effective treatment were defined as follows: intravesical pressure less than 40 cm H₂O, less than two incontinence events per day, bladder capacity of at least 300 ml, and bladder compliance greater than 25 ml/cm H₂O. The study terminology and the urodynamic parameters followed the International Continence Society guidelines [10].

2.3. Bladder diaries

All study participants were provided with a bladder diary to annotate catheterisation time and amount, time and amount of fluid intake, incontinence events and description, as well as occurrence of side-effects. The fluid intake recording was necessary to ensure patients' constant hydration during the study.

2.4. Statistical analysis

The data were collected with Excel (Microsoft Deutschland GmbH, Unterschleissheim, Germany) and analysed with JMP (SAS Institute, Cary, NC, USA). Wilcoxon and Kruskal-Wallis tests were used to compare results in each treatment group before and after addition of the second antimuscarinic drug. One-way analyses of variance (ANOVAs) with Tukey-Kramer honestly significant difference were used to compare effects in the three groups; a post hoc analysis was performed for individual changes in each parameter. *P* values of < 0.05 were considered statistically significant.

3. Results

3.1. Resultant medication

Group A (*n* = 8; mean age, 35.5 yr; SD ± 10.9) received 8 mg of tolterodine and oxybutynin dosages between 15 and 30 mg (Table 2). Group B (*n* = 11; mean age, 39.9 yr; SD ± 13.0) received 90 mg of trospium and tolterodine dosages between 4 and 8 mg. Group C (*n* = 8; mean age, 30.1 yr; SD ± 3.4) received 30 mg of oxybutynin and trospium dosages between 45 and 90 mg.

Table 3 – Side-effects and drop outs

	Group A	Group B	Group C
Dry mouth	2	3	2
Blurred vision	0	1	1
Dry skin	0	0	0
Discontinuation due to side-effects	1	1	
Discontinuation due to unsatisfactory outcome	1	1	

3.2. Reported side-effects

Seven patients reported side-effects under the combined therapy with two antimuscarinic drugs (Table 3). Five patients had only mild side-effects; therefore, the combined therapy was continued. The two remaining patients terminated the combined therapy at the end of the study because of the side-effects (one patient had severe dry mouth [group A], and another patient had distinct blurred vision [group B]), despite their attaining objective and subjective treatment success.

3.3. Drop outs

Two patients (one patient in group A, the other in group B) did not experience any satisfactory benefit or improvement under the combined antimuscarinic therapy (Tables 2 and 3), despite also receiving doubled medication for the second antimuscarinic drug.

3.4. Urodynamic results using combined drug strategy

In group A, the combined drug regimen reduced incontinence events from a range of 5 to 10 (median,

7), to zero to 2 (median, 0.5). The urodynamic examination verified an increase in reflex volume (from a median of 145 ml to 330) as well as an increase in maximal bladder capacity (195 to 380 ml) resulting from improved detrusor compliance (20 to 40 ml/cm H₂O). Group B demonstrated similar results: Reflex volume increased from a median of 120 ml to 300 ml, and improvement of maximal capacity from 200 ml to 400 ml was noted. Detrusor compliance advanced from 10 to 30 ml/cm H₂O. Patients' incontinence events decreased from a range of 5 to 14, to a range of 1 to 6. A similar outcome was seen in group C, in which the range of incontinence events decreased from 6 to 15, to zero to 2. In addition to increased reflex volume (median, 110 to 375 ml), the maximal capacity increased from 170 to 400 ml, with detrusor compliance increasing from 15 to 30 ml/cm H₂O. Table 4 provides mean values for all three groups (Figs. 1–3).

In addition to the improvement noted in all groups, no significant differences in the results between the three treatments were found with regard to detrusor compliance ($p = 0.97$) or incontinence events ($p = 0.11$). However, with regard to bladder capacity ($p < 0.01$, ANOVA), group A showed significantly lower improvement compared with the other groups. Amelioration of reflex volume ($p < 0.02$, ANOVA) was statistically higher in group C compared with group B ($p < 0.05$ each, Tukey-Kramer, Fig. 4).

The presented results are derived from the 1-mo evaluation. A final evaluation (diary and urodynamic) was performed at 6 mo, the results of which were almost identical to the 1-mo follow-up. As a result of this similarity, the 6-mo results were not reported separately.

Table 4 – Urodynamics and bladder diary analysis for group A (tolterodine + oxybutynin), group B (trospium + tolterodine), and group C (oxybutynin + trospium)

	Bladder diaries mean (±SD)		Urodynamics mean (±SD)					
	Incontinence events/day		Bladder capacity (ml)		Reflex volume (ml)		Detrusor compliance in (ml/cm H ₂ O)	
	Before	After	Before	After	Before	After	Before	After
Group A	7.0 (1.5)	0.6 (0.7)**	192.5 (54.7)	370 (71.1)*	141.3 (34.4)	326.3 (74.4)*	17.5 (7.1)	36.3 (5.2)*
Group B	7.5 (2.7)	2.0 (1.5)***	181.8 (42.6)	406.4 (52.0)***	125.5 (43.0)	297.3 (59.5)****	14.5 (5.2)	33.6 (5.0)****
Group C	8.6 (2.7)	1.3 (0.9)**	170.0 (31.2)	412.5 (42.3)**	123.8 (29.7)	368.8 (27.5)**	15.0 (5.3)	33.8 (5.2)**

SD, standard deviation.

* <0.005; ** <0.001; *** <0.0005; **** <0.0001.

"Before" amounts taken at onset of study and considered baseline; "after" amounts taken at 4-wk follow-up.

Differences between the 6-mo and 4-wk follow-up results were insignificant; therefore, they were not presented.

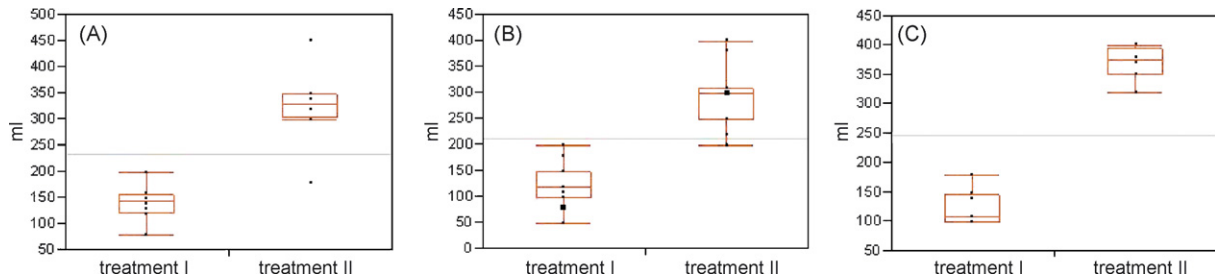


Fig. 1 – (A–C) Reflex volumes of single treatment (treatment I) and combined treatment (treatment II) in the three groups: (A) Tolterodine + oxybutynin as treatment II. (B) Trospium + tolterodine. (C) Oxybutynin + trospium.

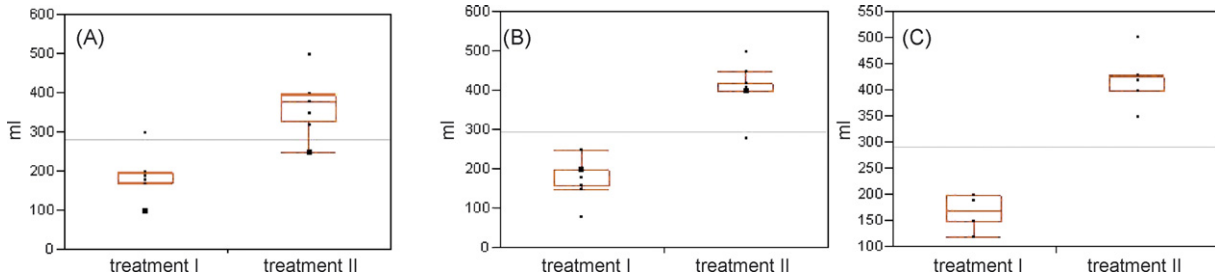


Fig. 2 – (A–C) Bladder capacity of single treatment (treatment I) and combined treatment (treatment II) in the three groups. (A) Tolterodine + oxybutynin as treatment II. (B) Trospium + tolterodine. (C) Oxybutynin + trospium.

4. Discussion

4.1. Antimuscarinics in the treatment of neurogenic bladder dysfunction

The use of antimuscarinic drugs as first-line therapy is well established, so normal bladder compliance can be achieved with the goal of protecting the upper urinary tract. The most important side-effect to address for the patient suffering from neurogenic bladder dysfunction is urine incontinence caused by involuntary urine leakage, which decreases the patient’s quality of life. Side-effects such as dry mouth, blurred vision, and bowel constipation are extensively described by various authors [11,12] and must be reconciled.

Trospium and oxubutynin, as characterised by Stohrer et al [13,14] and Frohlich et al [15], represent

drugs of the previous generation of antimuscarinics; however, they are still considered state-of-the-art in the therapeutic regimen of neurogenic bladder dysfunction. Tolterodine was also one of the first new-generation antimuscarinics that was better tolerated owing to reduced side-effects [16]. However, it must be noted that, with use of the aforementioned drugs at the manufacturer’s recommended dosage, approximately 30% of patients still do not experience sufficient efficacy [7,17].

4.2. Dosage-escalated antimuscarinic monotherapy

To offer these patients a more-effective treatment, we thought an alternative to the common medication treatment could be promising. Therefore, in a previous study at our clinic, patients with detrusor malfunctioning improved with dosage escalation up

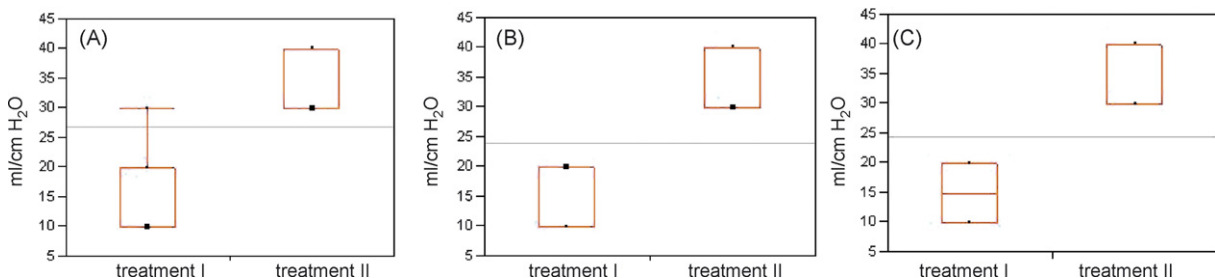


Fig. 3 – (A–C) Detrusor compliance of single treatment (treatment I) and combined treatment (treatment II) in the three groups. (A) Tolterodine + oxybutynin as treatment II. (B) Trospium + tolterodine. (C) Oxybutynin + trospium.

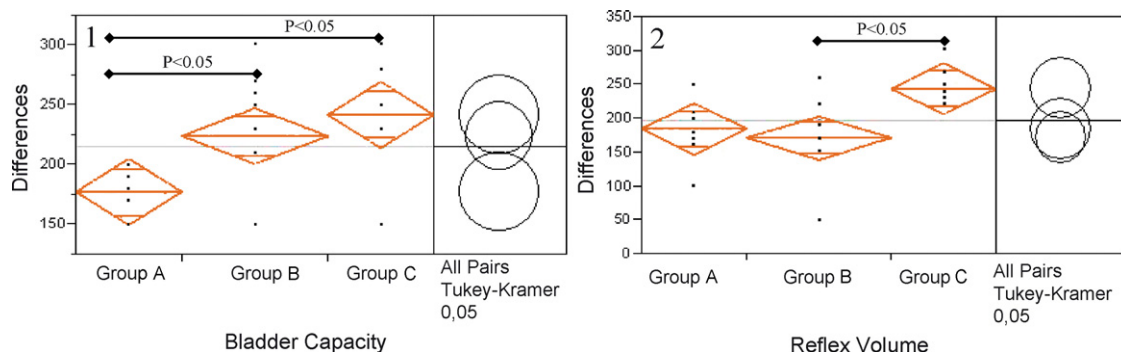


Fig. 4 – (1-2) Changes in bladder capacity (1) and reflex volume (2) within the three groups. Group A: tolterodine + oxybutynin as treatment II; group B: trospium + tolterodine; group C: oxybutynin + trospium.

to the doubled recommended dosage. Interestingly most of the patients reported fewer side-effects (such as dry mouth [20%]) than those reported in previously published studies; however, 24% of the patients were still unsatisfied by the treatment regimen [9].

4.3. Combined antimuscarinic treatment

As a result of patient dissatisfaction in the first study, we investigated using an additional antimuscarinic drug with a slightly different receptor interaction as a solution to ameliorating the outcome of this population. In the interests and comfort of our patients (demonstration of no or few side-effects), we decided to maintain the original doubled antimuscarinic and initiate a second antimuscarinic drug (from the initial study's set) in the second phase. This solution has not been previously reported to our knowledge; we have noted that combined therapies of an antimuscarinic drug with an α -blocker for treatment of lower urinary tract symptoms due to benign prostatic hyperplasia have recently been published by Novara et al [18], Irani [19], and Kaplan et al [20].

In the data (Table 4) for our three study groups, which were accomplished in a small population of specific patients, our statistical analysis demonstrates significant results with an increase in reflex volume, maximal bladder capacity, and detrusor compliance under the combined treatment. More importantly, the primary positive clinical outcome, which has increased patients' quality of life [21], was statistically demonstrated by a significant reduction in incontinence events. The patients' feedback confirmed that reduced frequency of incontinent events positively affected their quality of life.

Because all groups reached normal values for urodynamic parameters and patient satisfaction,

the minor differences found in comparisons of the three treatment groups may be disregarded. We noted that, for patients primarily suffering from very low bladder capacity, application of the treatment regimens of groups B or C resulted in a higher increase in capacity compared with group A (Fig. 4).

4.4. Combined antimuscarinic treatment rationale

As previously mentioned, studies from van Kerrebroeck et al [6] and Horstmann et al [9] demonstrated that increased administrations of antimuscarinic drugs were well tolerated. In light of these published data, we hypothesised that, since our patients did not experience a benefit from the doubled dosage in the first study, a different combination of antimuscarinics (with a modified receptor selectivity) might be beneficial and result in only a mild increase in side-effects. At the onset of the present study, most participants were concerned about possible increased side-effects from use of a second medication.

Chapple et al [22] noted that the M2-muscarinic receptor is the predominant receptor in the urinary bladder. M3-muscarinic receptors are represented in a lower amount but with amplified functionality. They also reported that pre-junctional-inhibiting M2- or M4-muscarinic receptors, as well as M1-muscarinic receptors, were detected in the urinary bladder. However, the interaction of the subdivision of these muscarinic receptors is currently unknown.

It is believed that a synergistic activation of different muscarinic receptors or interaction of receptors on different parts of the bladder wall might be one explanation for the present study's positive results. Another reason might be that the patients not experiencing sufficient efficacy might have undiscovered faster metabolism of antimus-

carinics, which requires an increased dosage of different antimuscarinic drugs. Further analysis may tell us that down-regulation of subdivisions of antimuscarinic receptors under a monotherapy may lead to better susceptibility of other subdivisions when treated by the second drug.

With regard to the relationship between side-effects and receptor selectivity, Andersson [23] published a report about the presence of muscarinic receptors in different tissues: M1-receptors in brain (cognition), sympathetic ganglia, and salivary glands; M2-receptors in cardiac tissue (heart frequency), brain, and smooth muscle (bladder and stomach); M3-receptors in salivary glands, eye, and especially smooth muscle (bladder contraction, intestinal movement, accommodation); M4-receptors in brain and salivary glands; and M5 receptors in brain, eye, and also urinary bladder. Goepel et al [24] looked for interaction of the different antimuscarinic drugs with the subset of receptors. Because tolterodine and trospium have not show any receptor selectivity, they noted that oxybutynin has an increased affinity to M1- and M3-receptors to the disadvantage of M2- and M5-receptors.

Interestingly, Halaska et al [25] and Madersbacher et al [26] reported better tolerability in patients using trospium versus oxybutynin at the same efficacy levels, even though oxybutynin has different affinities to the muscarinic receptors. Trospium with continuous affinity to all receptors (M1–5) showed milder side-effects.

4.5. Future studies

In the present study, the new generation of agents for management of bladder dysfunction such as darifenacin and solifenacin were not investigated. Darifenacin is characterised by receptor selectivity for M3 against M2 and moderate selectivity against M1, whereas solifenacin shows moderate selectivity for M3 against M2, similar to that described for oxybutynin [27,28]. We think that embedding these new drugs into a combined regimen for the patient group who do not receive enough benefit from the recommended dosage as well as escalating the dosages could further enrich treatment efficacy with reduced side-effects.

An additional aspect of this treatment option would be cognitive constriction with a combined oral medication. The effects of antimuscarinic drugs on the central nervous system are currently the focus of several investigation groups [29,30]. Studies of oxybutynin have shown a negative effect in elderly patients [31].

On the basis of our Medline review, we found no published explanation that supports the theses of receptor interaction by combined administration of antimuscarinics, with a moderate increase in tolerable side-effects. Furthermore, investigations and patient follow-up are necessary for verification of long-term efficacy, including an analysis of receptor selectivity and its interactions.

5. Conclusion

The results of this investigation demonstrate that the combination of antimuscarinic drugs in a higher-than-recommended dosage is an effective treatment option for incontinence in patients suffering from neurogenic bladder dysfunction, if the single-use antimuscarinic drug does not lead to satisfactory amelioration. Side-effects occurred equally in patients treated with only one antimuscarinic drug compared with the combined dosage. Further investigations are needed to collect data about long-term results and side-effects, especially concerning pharmacological and physiological aspects of the central nervous system.

Under short-term medical supervision, the described oral therapeutic regimen could be offered to compliant DSD patients before starting invasive treatments such as the injection of botulinum toxin [32] or intravesical application of drugs [33].

Conflicts of interest

The authors have nothing to disclose.

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