Advances in Urology

Overactive Bladder: Pathophysiology, Diagnostics, and Therapies

Guest Editors: John P. F. A. Heesakkers, Francisco Cruz, Yasuhiko Igawa, and Ervin Kocjancic

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Editorial Board

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Editorial

Overactive Bladder: Pathophysiology, Diagnostics, and Therapies

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This special issue on the overactive bladder deals with specific aspects of OAB with respect to pathophysiology, specific patient populations, and treatments. The editorial board selected 8 papers that address these special angles of the OAB spectrum.

In the basic research section, Y. Kubota et al. describe the role of KIT-positive cells in the urinary bladder. KIT staining is used as a marker for interstitial cells. Latest publications suggest that KIT is not only a detection marker of these cells but also may play a crucial role in the control of bladder function.

T. Antunes-Lopes et al. relate about the latest developments of biomarkers like nerve growth factor (NGF) and brain derived neurotrophic factor (BDNF) and how useful they are at this moment to be as biomarkers. It seems that BDNF is the best future candidate for this goal.

With respect to medical treatment, three papers are presented. The first is from A. Athanasopoulos and K. Giannitsas. In an overview about antimuscarinics, they conclude that the differences are small and that individuals respond differently to the various available drugs. A. Matsumori et al. illustrate that it is possible to prescribe other antimuscarinics when the first one fails. They present data about the effect of propiverine in patients who failed other antimuscarinic treatments for OAB. A special group of patients who are treated with OAB is presented by F. van Rey and J. Heesakkers. In a group of MS patients with OAB, the highly beneficial effect of solifenacin is presented based on bladder diaries and patient-reported outcome measures.

Another well-established treatment for OAB is pelvic electrical neuromodulation presented by T. F. Al-Shaiji et al. They review the indications, possible mechanisms of action, surgical aspects and possible complications, and safety issues of this technique.

A completely different type of neurostimulation for OAB is described by F. M. J. Martens et al. They relate about the results of the Finetech-Brindley neurostimulator in patients with a complete spinal cord injury. This difficult and time-consuming surgery has various beneficial effects on as well the urinary and the gastrointestinal tract. Moreover, the sexual functions and the lower limb spasms may change to the good with this exciting technique.

The last contribution in this special issue on OAB is from J. Neuhaus et al. They present about a fairly difficult and special kid on the block: those suffering from bladder pain syndrome or interstitial cystitis. They propose a new diagnostic model that includes extended diagnostics with molecular markers. Differential diagnosis and tailored therapy according to them should be based on three diagnostical columns: clinical diagnostics, histopathology, and molecular diagnostics. The future will tell whether this is way to go in this difficult-to-treat disturbance of the lower urinary tract.

The editorial board of this special issue hopes that these topics give you more insight in the OAB spectrum and that it gives new ideas to implement in basic research as well as clinical practice.

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Research Article

New Aspects in the Differential Diagnosis and Therapy of Bladder Pain Syndrome/Interstitial Cystitis

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Diagnosis of bladder pain syndrome/interstitial cystitis (BPS/IC) is presently based on mainly clinical symptoms. BPS/IC can be considered as a worst-case scenario of bladder overactivity of unknown origin, including bladder pain. Usually, patients are partially or completely resistant to anticholinergic therapy, and therapeutical options are especially restricted in case of BPS/IC. Therefore, early detection of patients prone to develop BPS/IC symptoms is essential for successful therapy. We propose extended diagnostics including molecular markers. Differential diagnosis should be based on three diagnostical "columns": (i) clinical diagnostics, (ii) histopathology, and (iii) molecular diagnostics. Analysis of molecular alterations of receptor expression in detrusor smooth muscle cells and urothelial integrity is necessary to develop patient-tailored therapeutical concepts. Although more research is needed to elucidate the pathomechanisms involved, extended BPS/IC diagnostics could already be integrated into routine patient care, allowing evidence-based pharmacotherapy of patients with idiopathic bladder overactivity and BPS/IC.

1. Introduction

There is an ongoing lively discussion about the diagnosis of interstitial cystitis (IC). Diagnosis mainly relies on clinical symptoms, since it has been shown that the more restrictive definition of the National Institute of Diabetes, Digestive, and Kidney Diseases (NIDDK) [1] failed to detect about 60% of the clinically significant IC patients [2]. Recently, IC has been redefined by the European Society for the Study of Interstitial Cystitis (ESSIC), which felt that bladder pain or discomfort to be most important criterion for differential diagnosis and inaugurated the term bladder pain syndrome/interstitial cystitis (BPS/IC) [3]. However, a number of alterations within the bladder wall, regarding detrusor smooth muscle cells [4–7], suburothelial myofibroblasts [8–10], innervation [11–14], urothelial function and integrity [15–19], and cytokine expression [20, 21], have been described, implying that pain symptoms develop relatively late in the cause of the disease. We hypothesize that initial urothelial impairment (unknown origin) initiates a pathophysiological cascade leading in long-term to the development of BPS/IC, and that severe pain symptoms are only present in late phase, that is, full blown clinical picture (Figure 1).

If patients could be detected at an early stage of the disease, the chance of successful therapeutical intervention would improve. Therefore, we examined patients showing clinical symptoms of BPS/IC to find a pattern of alterations associated with BPS/IC.

Since the whole bladder wall seems to be involved in bladder dysfunction, it is necessary to evaluate urothelial integrity, detrusor smooth muscle cell receptor expression, alterations in the lamina propria, and afferent nervous control. We here propose a diagnostic approach integrating three diagnostic "columns", (i) clinical diagnosis, (ii) histopathology, and (iii) molecular diagnostics.

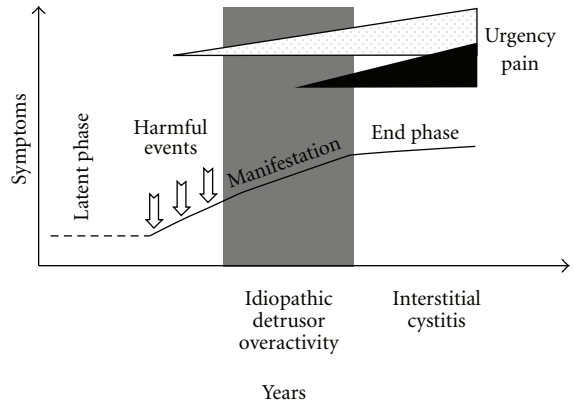


Figure 1: Hypothetical course of BPS/IC development. While urgency develops in early "manifestation" phase, pain symptoms become evident only in late "end" phase, defining full-blown BPS/IC.

2. Materials and Methods

The study was approved by the local Ethics Committee of the University of Leipzig and followed the recommendations of the Helsinki declaration (1964).

Female patients from our hospital were included into a preliminary study of receptor expression analysis; BPS/IC: $n = 19$; age 61.95 (3.164) years, mean (SEM); ESSIC classification: 2A (0), 2B (4), 2C (8), 2X (7); control: $n = 9$; age 63.19 (3.019) years; female patients undergoing cystectomy due to bladder carcinoma or gynecological tumors. In a second study, we compared the expression of human chorionic gonadotropin; control: $n = 5$; age 62.00 (4.615) years; BPS/IC: $n = 10$; age 59.50 (1.881) years; ESSIC classification CX (4), 2A (1), 2B (1), 2C (2), and 2X (2).

We used confocal immunofluorescence analysis to quantify the expression of muscarinic (M2, M3), purinergic (P2X1, P2X2, P2X3), histamine (H1, H2) receptors, and HCG-beta (Table 1) and used SYBR-green quantitative real-time PCR to examine receptor gene expression (Table 2). Confocal images were acquired at a Pascal 5 laser scanning microscope equipped with a 63×1.4 na oil immersion objective (Zeiss, Jena, Germany). Analyses were done using self written ImageJ [22] scripts, OpenOffice (http://www.OpenOffice.org/), and GraphPad Prism version 5 for Mac OS X (GraphPad Software, San Diego, Calif, USA, http://www.graphpad.com/) was used for statistics.

3. Results and Discussion

3.1. Symptoms of Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC). Clinically, frequency, urgency, and bladder pain are characteristic for patients suffering from IC. In the early stages of the disease, urgency seems to be the most impressive symptom, and bladder pain develops in later phase, probably in conjunction with advanced urothelial damage and perineuronal inflammation (Figure 1). In the "latent" and early "manifestation" phase, it is essential to distinguish motoric detrusor overactivity from developing BPS/IC. Urodynamics can help to perform differential diagnosis; however, urgency reported by the patient does not always correlate with urodynamical findings. Therefore, we suspect a significant part of the patients diagnosed with OAB syndrome to suffer from an early stage of BPS/IC.

An indirect proof for the significance of urothelial damage for the pathophysiology of the OAB syndrome comes from a study showing higher rate of symptoms improvement after additional application of chondroitin sulfate than by anticholinergic therapy alone [23]. Chondroitin sulfate is instilled into the bladder to restore the glycosaminoglycan (GAG) layer of the urothelium, which is part of the protective urine-tissue barrier of the intact urothelial lining [19]. Therefore, urothelial lesion seems to be the best candidate event for initialization of chronic abacterial cystitis. In case of therapeutical failure of anticholinergics, differential diagnostics of BPS/IC should be performed.

3.2. The Three "Columns" of IC-Diagnostics. We feel that it is essential to early include histopathological and molecular biological examination of bladder biopsies into the diagnostic regime. Since all cellular components of the bladder seem to be involved in pathophysiology of BPS/IC, only histological examination of deep biopsy, spanning the whole bladder wall, ensures proper diagnosis.

(i) Cystoscopy. Despite common patient symptom report, frequency, urgency, and bladder pain, the cystoscopic picture of the bladder might vary considerably (Figure 2). Only in two cases, cystoscopic evaluation would support BPS/IC diagnosis (Figures 2(b) and 2(c)), while the other bladder shows hypervascularization (Figure 2(a)).

Despite this heterogenic cystoscopic appearance, the endoscopic evaluation of the bladder mucosa including the vascularization status reveals valuable information. Therefore, cystoscopy should be included into the diagnostic routine for OAB diagnostics. The description of a pathological cystoscopic findings is essential for early therapeutical conception before pain becomes the dominant symptom of a uncontrollable disease. During this stage of disease often, a clinically hard-to-define urgency component dominates, which is, therefore, referred to as "idiopathic urgency".

Due to the fact that BPS/IC is mostly regarded as pain syndrome and not as a disease associated with the end organ urinary bladder, cystoscopic diagnostics and bladder provocation tests, which are able to detect defects in the urothelial layer, have come out of focus recently. Therefore, in the next chapters, we will discuss the relevance of histopathological alterations within the bladder wall for the differential diagnosis of BPS/IC. There are two contrary diagnostic approaches, the strategy to pure clinical diagnostics and the concept to evaluate pathological alterations in the different functional units of the bladder wall, which requires, however, invasive diagnostics.

(ii) Histopathology. Histopathological examination should be obligatory to enable exclusion of carcinoma in situ (cis). There is no common histomorphological appearance of IC [24–26]. In the early stage of disease, the urothelial lining might be normal, and mastocytosis of the detrusor, initially

Table 1: Antibodies used in indirect confocal immunofluorescence.

(a) Primary antibodies

Primary antibodies	Host	Source	Order no.	Dilution
M2, muscarinic receptor	rabbit	[1]	AS-3721S	1 : 1000
M3, muscarinic receptor	rabbit	[1]	AS-3741S	1 : 1000
P2X1, purinergic receptor	rabbit	[2]	ab10248	1 : 1000
P2X2, purinergic receptor	rabbit	[2]	ab10266	1 : 1000
P2X3, purinergic receptor	rabbit	[2]	ab10269	1 : 1000
H1, human histamine receptor 1	rabbit	[3]	H1R12-A	1 : 250
H2, human histamine receptor 2	rabbit	[3]	H2R22-A	1 : 250
HCG (beta-1 epitope)	mouse, IgG1	[5]	MCA19	1 : 500
HCG (beta-2 epitope)	mouse, IgG1	[5]	MCA329	1 : 20
alpha-smooth muscle cell actin	mouse, IgG2a	[4]	A2547	1 : 2000

(b) Secondary antibodies

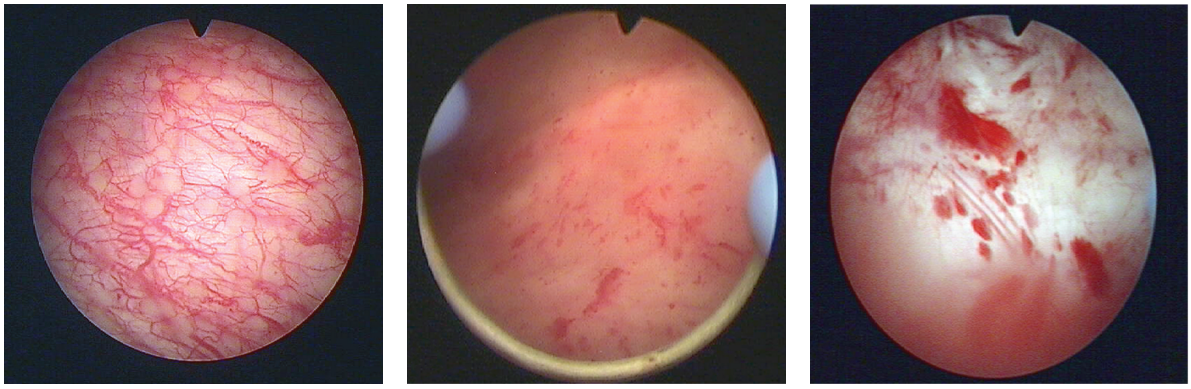
Secondary antibodies	Source	Order no.	Dilution
Alexa Fluor 488 goat antimouse IgG2a	invitrogen	A-21131	1 : 500
Alexa Fluor 555 goat antirabbit	invitrogen	A-21428	1 : 500
Alexa Fluor 555 goat antimouse	invitrogen	A-21127	1 : 500

[1] Research & Diagnostic Antibodies, North Las Vegas, USA.
[2] Abcam Inc., Cambridge, USA.
[3] Alpha Diagnostic Intl. Inc., San Antonio, USA.
[4] Sigma-Aldrich Chemie GmbH, Steinheim, Germany.
[5] AbD Serotec, MorphoSys AG, Martinsried/Planegg, Germany.

Table 2: Primers used for real-time PCR.

Primer	Sequence 5′ → 3′	Product length (bp)	Binding site	AccNo
h36B4 forward	AACATGCTCAACATCTCCCC	397	exon 6	NR_002775.1
h36B4 reverse	CCGACTCCTCCGACTCTTC		exon 8	
aSMCA forward	CCAACTGGGACGACATGGAAA	212	exon 4	NM_001613.2
aSMCA reverse	GCGTCCAGAGGCATAGAGAGACA		exon 6	
M2 forward	CTAAGCAAACATGCATCAGAATTGG	288	exon 6	NM_001006632.1
M2 reverse	AAGGTGCACAAAAGGTGTTAATGAG		exon 6	
M3 forward	ACCCAGCTCCGAGCAGATGGAC	341	exon 5	NM_000740.2
M3 reverse	CGGCTGACTCTAGCTGGATGGG		exon 5	
P2×1 forward	GCGTAATAAGAAGGTGGGCGTTA	109	exon 1	NM_002558.2
P2×1 reverse	GCCGCTCGAGGTCTGGTA		exon 2	
P2×2 forward	CAGGTTTGCCAAATACTACAAGATCA	105	exon 8	NM_174873.1
P2×2 reverse	AACTTCCCGGCCTGTCCAT		exon 9	
P2×3 forward	TCTTCACCTATGAGACCACCAAGTC	83	exon 1	NM_002559
P2×3 reverse	GATCAGAAGCTGAACTACTCGGTTGAT		exon 1	
H1 forward	AAGTCACCATCCCAAACCCCCAAG	151	exon 3	NM_001098213
H1 reverse	TCAGGCCCTGCTCATCTGTCTTGA		exon 3	
H2 forward	AGGAACGAGACCAGCAAGGGCAAT	198	exon 2a	NM_022304
H2 reverse	GGTGGCTGCCTTCCAGGAGCTAAT		exon 2a	

h36B4 = human acidic ribosomal protein P0; aSMCA = alpha-smooth muscle cell actin.



(a) (b) (c)

Figure 2: Cystoscopic images of patients showing identical BPS/IC symptoms. Note the heterogeneity of the appearance of the mucosa and the differences in vascularization. (a) Hypervascularization of the bladder wall. (b) Atrophic bladder wall with petechial bleedings after bladder distension. (c) Ulcerative form of BPS/IC.

used to define BPS/IC [2, 27], might be absent even in late, full-blown BPS/IC. An early-stage nonulcerative form (i.e., Figures 2(a) and 2(b)) can be discerned from a late-stage ulcerative form (Figure 2(c)). Histopathological findings supporting the diagnosis of BPS/ICare the following.

(1) Urothelial lesions may be present as loss of covering umbrella cells, urothelial flattening, or urothelial denudation. The characteristic finding of urothelial cracking after hydrodistention can be ascribed to those histopathological alterations of the urothelial covering of the bladder wall.

(2) Fibrosis of the mucosa, often reaching the muscular layer is found especially in late stages of BPS/IC and accounts for reduced bladder capacity. The fibrosis proceeds with the progression of the disease and is related to chronic inflammation of the bladder wall.

(3) Interstitial chronic lymphoplasmacellular infiltration of the lamina propria is a characteristic finding in most of the patients. In addition, about 70% of the BPS/IC patients show perineuronal inflammation [26, 28, 29]. Especially at later stages of the disease, inflammatory infiltrates are also present within the detrusor muscle. However, mastocytosis of the mucosa and the detrusor muscle, which has been regarded as BPS/IC-specific feature [30, 31], seems to be not necessarily associated with BPS/IC [2, 24, 32].

(4) Nerve fiber proliferation in the lamina propria and the detrusor muscle is another common histopathological finding in BPS/IC and is regarded as a major neuropathological factor [11, 33, 34]. However, despite neural upregulation contributes to the pathophysiology of BPS/IC, it is still unclear whether it is a causative factor of BPS/IC or an after-effect.

(5) Hypovascularization of the urothelial layer has been described [35] and may account for impaired bladder perfusion [36, 37] along with wall thickening of small blood vessels in the submucosa and edematous alterations.

(iii) Molecular Diagnostics. Few studies examined regulation of neurotransmitter receptors in the normal and diseased human bladder. Alterations of receptor expression on various cells of the bladder wall including nerve fibers have been demonstrated in OAB [38, 39], idiopathic detrusor overactivity (IDO) [4, 34, 40], neurogenic bladder [41], and interstitial cystitis [5, 12].

Since muscarinic receptors on detrusor smooth muscle cells are the classical target for anticholinergic therapy, we included the expression of M2 and M3 subtypes in the receptor analysis of the detrusor. In addition, purinergic signaling is the second major contributor to detrusor mass contraction. Atropine-resistant, ATP-mediated detrusor contractions have been shown to increase with age [42]. Histamine can evoke calcium transients in cultured human detrusor smooth muscle cells [43], and histamine receptors have been the target of IC therapy with H1 [44] or H2 [45] selective antihistaminics. Therefore, we routinely analyze the expression of muscarinic (M2, M3), purinergic (P2X1, P2X2, P2X3), and histamine (H1, H2) receptors in the detrusor smooth muscle cells by confocal immunofluorescence. In double immunolabeling with alpha-smooth muscle cell actin (aSMCA), which is located directly beneath the cellular membrane of detrusor myocytes, quantification of receptor immunofluorescence could be restricted to receptors located in cell membrane. Individual receptor expression profiles are generated (Figure 3), and based on those, we developed a tailored therapy concept.

The use of routine formalin-fixed bladder tissue has the advantage that there is no need for sophisticated probe preparation and retrospective studies can be conducted on archive material.

The concept of tailored therapy based on molecular diagnostics has already been established for other disease entities, for example, colon carcinoma [46], and is a most promising approach in cancer management [47].

We also used quantitative real-time PCR (qPCR) to address receptor gene expression. However, we found no correlation between qPCR and protein expression (data not shown), which is in agreement with the literature [4, 48].

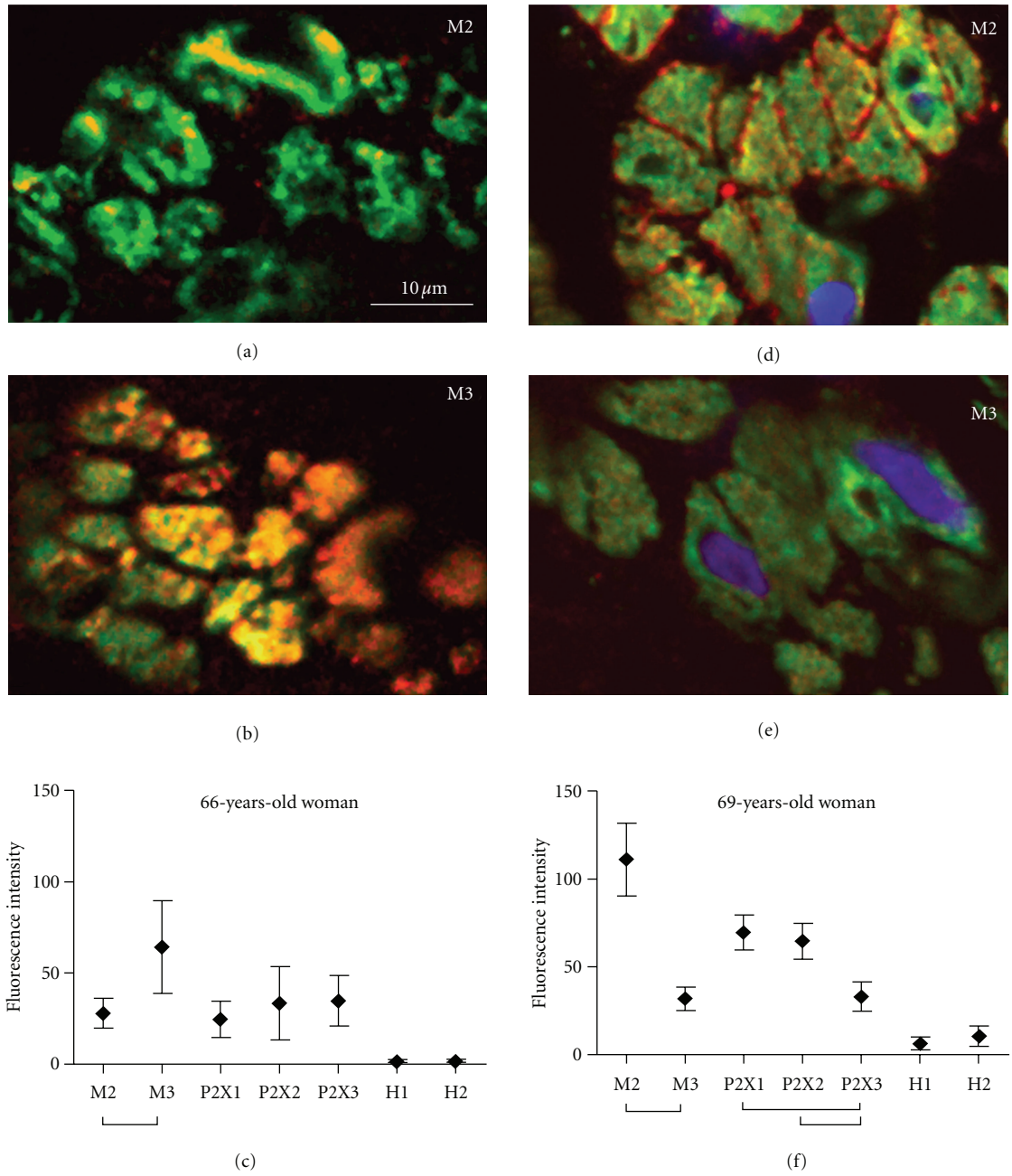


Figure 3: Examples of individual receptor expression profiles based on confocal immunofluorescence analysis. (a–c) showing a female patient with overexpression of M3, P2X1-3 receptors; (d–f) typical distribution in IC patients with overexpression of M2 receptor; in addition, this patient shows high levels of purinergic receptors and significant expression of histamine H2 receptor; aSMCA (green); receptor staining (red); nuclear staining (blue); bar in (a) applies to all micrographs; (c, f) mean ± SD; bars indicate significant differences (ANOVA, Tukey's Test, $P < 0.05$).

(1) *BPS/IC Patients Show a Distinct Detrusor Muscle Receptor Pattern*. Confocal immunofluorescence-based receptor profiling revealed distinct upregulation of muscarinic (M2) and purinergic (P2X1, P2X2) receptors in BPS/IC patients compared to the control group (Figure 4).

(2) *Muscarinic Receptors*. BPS/IC bladders showed significant upregulation of muscarinic M2 receptor ($P = 0.0105$, Mann-Whitney test), which was also significantly higher than the M3 receptor in the detrusor of those patients ($P = 0.0021$, Wilcoxon signed rank test). In contrast, control detrusor showed equal expression of M2 and M3 receptors. In a small fraction of patients (3/19 patients, 16%), the M3 receptor expression was significantly higher than that of M2 muscarinic receptor. Numerous studies have shown that M3 selective anticholinergics are not superior to nonselective anticholinergic in respect to reduction

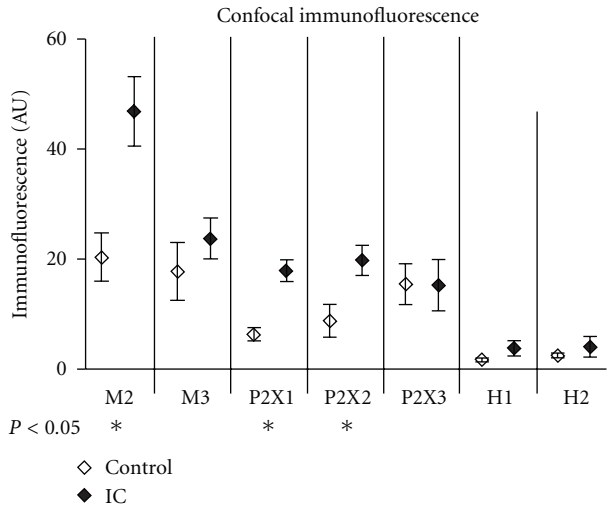


Figure 4: Comparison of the receptor expression in detrusor biopsies from age-matched patient collectives (control $n = 9$; BPS/IC $n = 19$). P values < 0.05 were considered significant (Mann-Whitney nonparametric statistical test).

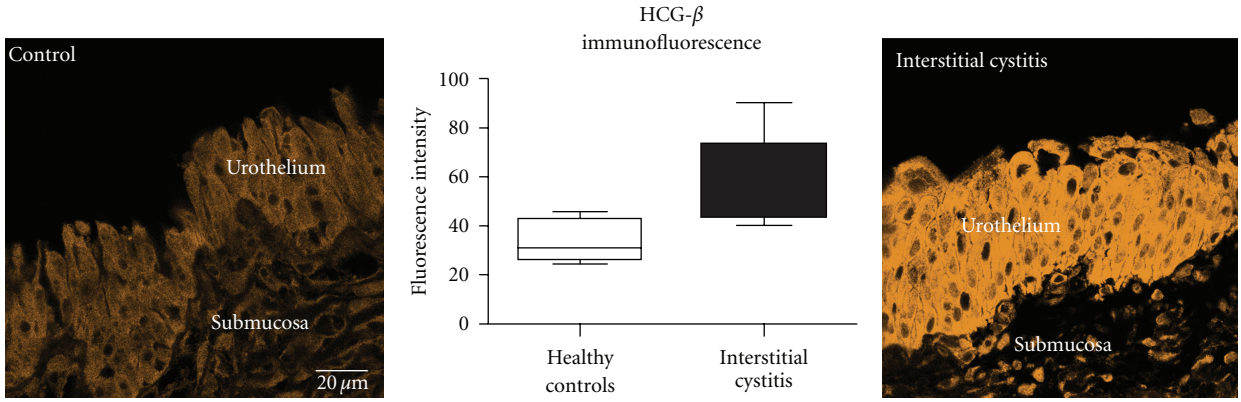


Figure 5: HCG-beta (beta-2 epitope) immunoreactivity in urothelium. (a) Control bladder from a 36-year-old woman, gynecologic tumor, no bladder carcinoma; (c) BPS/IC bladder of a 53-year-old woman showing extreme upregulation of HCG-beta; bar in (a) applies to (a and b); (c) Quantitative analysis revealed significant differences between female controls ($n = 5$) and female BPS/IC ($n = 10$) patients (Mann-Whitney test, $P < 0.05$).

of OAB symptoms. We suppose that this might in part be due to heterogeneity in muscarinic receptor expression in the patients collectives examined. Preselection of patients by their M2/M3 receptor expression status might, therefore, improve anticholinergic therapy.

(3) *Purinergic Receptors*. Purinergic P2X receptors are expressed on detrusor smooth muscle cells and mediate atropine-resistant, ATP-evoked detrusor contractions [49, 50]. Unfortunately, to date, subtype selective antipurinergic drugs are not available for therapy. However, patients with overexpression of P2X receptors showed good response to botulinum-toxin A (BoNT-A) injection therapy. BoNT-A is thought to inhibit both efferent motor nerves and afferent sensory nerve [51]. Our own preliminary studies of BoNT-A effect on the receptor expression in the bladder speak in favor of a modulation of receptor expression in detrusor smooth muscle cells (preliminary report [52]).

(4) *Histamine Receptors*. In our collective, both H1 and H2 histamine receptor subtypes were slightly upregulated (Figure 4), however, without reaching significance level. The expression showed high individual variability (H1 > H2 (6); H1 = H2 (10); H2 > H1 (3)) and 3 patients showed exceptionally high histamine receptor expression in the range of M3 or purinergic receptor expression. Antihistaminic therapy using H1-selective or H2-selective antihistaminic drugs was based on the finding of enhanced mast cell infiltration in IC patients [53]. Unfortunately, the outcome of the studies varied considerably.

Therefore, antihistaminic therapy has not been established widely as therapeutic option. Histamine receptors are expressed in detrusor smooth muscle cells and might be highly overexpressed in individual cases. Histamine can evoke calcium transients in cultured human bladder smooth muscle cells [43, 54] and detrusor contractions [55]. Therefore, antihistaminics may act directly on detrusor smooth muscle cells. The heterogeneity of histamine receptor expression may well account for the high variability of therapeutical success. In case of upregulation, H1 or rather H2 antagonists would promise maximal effect of antihistaminic therapy, which might be used in combination with receptor expression-adapted anticholinergics.

(5) *Molecular Diagnostics of the Bladder Urothelium*. BPS/IC is a disease of the complete bladder wall, including detrusor, submucosa, and urothelium. Therefore, it is essential to include pathology of the different cellular components into BPS/IC differential diagnosis. Despite pathology of the urothelium are most prominent in cystoscopic examination and breakdown of the urothelial urine-tissue barrier is well recognized as major pathophysiological factor in BPS/IC, cellular alterations have not been investigated intensively. Based on our own clinical experience, we examined the expression of human chorionic gonadotropin beta (HCG-beta) in the urothelium of BPS/IC and control patients. An interesting, still not explainable phenomenon is the clinical observation that IC symptoms ameliorate in female patients during pregnancy or infertility treatment with (HCG-beta). We found expression of HCG-beta in the urothelium throughout the urinary tract. Interestingly, HCG-beta is expressed in females and males, which indicates a new, unknown function of this hormone. HCG-beta can no longer be regarded as pregnancy-related hormone or tumor marker, since meanwhile our research group found constitutive expression of HCG-beta in bowel and eye (unpublished data). Two distinct HCG-beta isoforms, which are coded by different genes: type 1 (HCG-beta 6,7) and type 2 (HCG-beta 3,5,8) are differentially expressed throughout the body [56]. While type 2 is expressed in placenta and in malignant tumors, type 1 is expressed in nontrophoblast tissues. It is especially interesting that the endometrial production of HCG-beta varies in the female during normal menstrual cycle, reaching maximal concentrations in the late secretion phase [57, 58]. The effect of HCG-beta in the endometrium includes cell differentiation and neovascularization and might serve as a model for the restoration of urothelial lining in BPS/IC. In a preliminary study, we found upregulation of HCG-beta in the urothelium of nonpregnant BPS/IC women and also in men (Figure 5). Restoration of the destructed urothelial barrier in BPS/IC could be promoted by HCG-beta therapy and would be a causal therapeutical concept.

4. Conclusions

BPS/IC is a complex bladder dysfunction involving all cellular layers of the bladder. Current medicinal therapies lack consistent success. We propose a diagnostical concept including cystoscopic examination, histopathological evaluation, and the assessment of neurotransmitter expression profile to develop a tailored BPS/IC therapy.

Based on the expression levels of muscarinic receptors, it seems likely that patients with M3 receptor overexpression would profit most from M3 selective anticholinergics, while unselective anticholinergics may be the better choice for patients showing high levels of M2 receptors, as found in the majority of BPS/IC patients in our study. In case of significant histamine receptor expression, subtype selective antihistaminic therapy should be tried. Patients resistant to anticholinergic therapy might also profit from BoNT-A injection therapy, which might be a good choice especially if purinergic receptors are overexpressed. We further propose the evaluation of human chorionic gonadotropin expression in urothelial cells, which might lead to new therapeutical options for BPS/IC treatment.

To date, it seems likely that BPS/IC patients would profit most from combination of various receptor inhibitors adapted to their individual receptor profile. In addition, urothelial regeneration could be the clue to long-lasting success in BPS/IC therapy. There is a urgent need for clinical studies to verify the benefit of tailored therapy concept proposed here.

Acknowledgments

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References

[1] J. Y. Gillenwater and A. J. Wein, "Summary of the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases Workshop on Interstitial Cystitis, National Institutes of Health, Bethesda, Maryland, August 28-29, 1987," *Journal of Urology*, vol. 140, no. 1, pp. 203–206, 1988.

[2] P. M. Hanno, J. R. Landis, Y. Matthews-Cook, J. Kusek, and L. Nyberg, "The diagnosis of interstitial cystitis revisited: lessons learned from the National Institutes of Health interstitial cystitis database study," *Journal of Urology*, vol. 161, no. 2, pp. 553–557, 1999.

[3] J. P. van de Merwe, J. Nordling, P. Bouchelouche et al., "Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: an ESSIC proposal," *European Urology*, vol. 53, no. 1, pp. 60–67, 2008.

[4] K. J. Mansfield, L. Liu, K. H. Moore, K. J. Vaux, R. J. Millard, and E. Burcher, "Molecular characterization of M2 and M3 muscarinic receptor expression in bladder from women with refractory idiopathic detrusor overactivity," *BJU International*, vol. 99, no. 6, pp. 1433–1438, 2007.

[5] G. Mukerji, Y. Yiangou, J. Grogono et al., "Localization of M2 and M3 Muscarinic Receptors in Human Bladder Disorders and Their Clinical Correlations," *Journal of Urology*, vol. 176, no. 1, pp. 367–373, 2006.

[6] J. Neuhaus, F. Pfeiffer, H. Wolburg, L. C. Horn, and W. Dorschner, "Alterations in connexin expression in the bladder of patients with urge symptoms," *BJU International*, vol. 96, no. 4, pp. 670–676, 2005.

[7] V. Tyagi, B. J. Philips, R. Su et al., "Differential expression of functional cannabinoid receptors in human bladder detrusor and urothelium," *Journal of Urology*, vol. 181, no. 4, pp. 1932–1938, 2009.

[8] M. R. Ruggieri, "Mechanisms of disease: role of purinergic signaling in the pathophysiology of bladder dysfunction," *Nature Clinical Practice Urology*, vol. 3, no. 4, pp. 206–215, 2006.

[9] A. Roosen, S. N. Datta, R. A. Chowdhury et al., "Suburothelial myofibroblasts in the human overactive bladder and the effect of botulinum neurotoxin type A treatment," *European Urology*, vol. 55, no. 6, pp. 1440–1449, 2009.

[10] C. H. Fry, G. P. Sui, A. J. Kanai, and C. Wu, "The function of suburothelial myofibroblasts in the bladder," *Neurourology and Urodynamics*, vol. 26, no. 6, pp. 914–919, 2007.

[11] O. Nazif, J. M. H. Teichman, and G. F. Gebhart, "Neural upregulation in interstitial cystitis," *Urology*, vol. 69, no. 4, pp. S24–S33, 2007.

[12] J. E. Marchand, G. R. Sant, and R. M. Kream, "Increased expression of substance P receptor-encoding mRNA in bladder biopsies from patients with interstitial cystitis," *British Journal of Urology*, vol. 81, no. 2, pp. 224–228, 1998.

[13] S. Palea, W. Artibani, E. Ostardo, D. G. Trist, and C. Pietra, "Evidence for purinergic neurotransmission in human urinary bladder affected by interstitial cystitis," *Journal of Urology*, vol. 150, no. 6, pp. 2007–2012, 1993.

[14] T. J. Christmas, J. Rode, C. R. Chapple, E. J. G. Milroy, and R. T. Turner-Warwick, "Nerve fibre proliferation in interstitial cystitis," *Virchows Archiv*, vol. 416, no. 5, pp. 447–451, 1990.

[15] Y. Sun and T. C. Chai, "Up-regulation of P2X3 receptor during stretch of bladder urothelial cells from patients with interstitial cystitis," *Journal of Urology*, vol. 171, no. 1, pp. 448–452, 2004.

[16] H. V. Tempest, A. K. Dixon, W. H. Turner, S. Elneil, L. A. Sellers, and D. R. Ferguson, "P2X2 and P2X3 receptor expression in human bladder urothelium and changes in interstitial cystitis," *BJU International*, vol. 93, no. 9, pp. 1344–1348, 2004.

[17] P. J. Hauser, M. G. Dozmorov, B. L. Bane, G. Slobodov, D. J. Culkin, and R. E. Hurst, "Abnormal expression of differentiation related proteins and proteoglycan core proteins in the urothelium of patients with interstitial cystitis," *Journal of Urology*, vol. 179, no. 2, pp. 764–769, 2008.

[18] C. L. Parsons, "The role of the urinary epithelium in the pathogenesis of interstitial cystitis/prostatitis/urethritis," *Urology*, vol. 69, no. 4, pp. S9–S16, 2007.

[19] R. E. Hurst, R. M. Moldwin, and S. G. Mulholland, "Bladder defense molecules, urothelial differentiation, urinary biomarkers, and interstitial cystitis," *Urology*, vol. 69, no. 4, pp. S17–S23, 2007.

[20] P. Tyagi, D. Barclay, R. Zamora et al., "Urine cytokines suggest an inflammatory response in the overactive bladder: a pilot study," *International Urology and Nephrology*, vol. 42, no. 3, pp. 629–635, 2010.

[21] D. R. Erickson, S. X. Xie, V. P. Bhavanandan et al., "A comparison of multiple urine markers for interstitial cystitis," *Journal of Urology*, vol. 167, no. 6, pp. 2461–2469, 2002.

[22] W. S. Rasband and J. Image, US National Institutes of Health, Bethesda, Maryland, USA, 1997–2006 http://rsb.info.nih.gov/ij/.

[23] A. Gauruder-Burmester and G. Popken, "Follow-up at 24 months after treatment of overactive bladder with 0.2% sodium chondroitin sulfate," *Aktuelle Urologie*, vol. 40, no. 6, pp. 355–359, 2009.

[24] E. Kelada and A. Jones, "Interstitial cystitis," *Archives of Gynecology and Obstetrics*, vol. 275, no. 4, pp. 223–229, 2007.

[25] A. Rosamilia, Y. Igawa, and S. Higashi, "Pathology of interstitial cystitis," *International Journal of Urology*, vol. 10, pp. S11–S15, 2003.

[26] E. M. Messing and T. A. Stamey, "Interstitial cystitis. Early diagnosis, pathology, and treatment," *Urology*, vol. 12, no. 4, pp. 381–392, 1978.

[27] G. R. Sant, D. Kempuraj, J. E. Marchand, and T. C. Theoharides, "The mast cell in interstitial cystitis: role in pathophysiology and pathogenesis," *Urology*, vol. 69, no. 4, pp. S34–S40, 2007.

[28] S. L. Johansson and M. Fall, "Clinical features and spectrum of light microscopic changes in interstitial cystitis," *Journal of Urology*, vol. 143, no. 6, pp. 1118–1124, 1990.

[29] B. H. Smith and L. P. Dehner, "Chronic ulcerating interstitial cystitis (Hunner's ulcer). A study of 28 cases," *Archives of Pathology*, vol. 93, no. 1, pp. 76–81, 1972.

[30] W. L. Lynes, S. D. Flynn, L. D. Shortliffe et al., "Mast cell involvement in interstitial cystitis," *Journal of Urology*, vol. 138, no. 4, pp. 746–752, 1987.

[31] S. Larsen, S. A. Thompson, and T. Hald, "Mast cells in interstitial cystitis," *British Journal of Urology*, vol. 54, no. 3, pp. 283–286, 1982.

[32] T. C. Theoharides and G. R. Sant, "The mast cell as a neuro-immunendocrine effector in interstitial cystitis," in *Interstitial Cystitis*, G. Sant, Ed., pp. 101–108, Lippincott-Raven, Philadelphia, Pa, USA, 1997.

[33] X. Pang, J. Marchand, G. R. Sant, R. M. Kream, and T. C. Theoharides, "Increased number of substance P positive nerve fibres in interstitial cystitis," *British Journal of Urology*, vol. 75, no. 6, pp. 744–750, 1995.

[34] G. Mukerji, Y. Yiangou, S. K. Agarwal, and P. Anand, "Increased cannabinoid receptor 1-immunoreactive nerve fibers in overactive and painful bladder disorders and their correlation with symptoms," *Urology*, vol. 75, no. 6, pp. 1514–e15, 2010.

[35] T. Schwalenberg, J. Neuhaus, L. C. Horn et al., "New insights in the differential diagnosis of bladder pain syndrome," *Aktuelle Urologie*, vol. 41, no. 2, pp. 107–118, 2010.

[36] P. Irwin and N. T. M. Galloway, "Impaired bladder perfusion in interstitial cystitis: a study of blood supply using laser Doppler flowmetry," *Journal of Urology*, vol. 149, no. 4, pp. 890–892, 1993.

[37] M. A. Pontari, P. M. Hanno, and M. R. Ruggieri, "Comparison of bladder blood flow in patients with and without interstitial cystitis," *Journal of Urology*, vol. 162, no. 2, pp. 330–334, 1999.

[38] J. Neuhaus, T. Schwalenberg, N. Schlichting, M. Schulze, L. C. Horn, and J. U. Stolzenburg, "New methods of patient selection for improved anticholinergic therapy," *Urologe A*, vol. 46, no. 9, pp. 1202–1206, 2007.

[39] N. Hinata, T. Shirakawa, H. Okada, B. Achaya, S. Kamidono, and A. Gotoh, "Quantitative analysis of the levels of expression of muscarinic receptor subtype RNA in the detrusor muscle of patients with overactive bladdler," *Molecular Diagnosis*, vol. 8, no. 1, pp. 17–22, 2004.

[40] L. Liu, K. J. Mansfield, I. Kristiana, K. J. Vaux, R. J. Millard, and E. Burcher, "The molecular basis of urgency: regional difference of vanilloid receptor expression in the human

urinary bladder," *Neurourology and Urodynamics*, vol. 26, no. 3, pp. 433–438, 2007.

[41] C. M. Brady, A. Apostolidis, Y. Yiangou et al., "P2X3-immunoreactive nerve fibres in neurogenic detrusor overactivity and the effect of intravesical resiniferatoxin," *European Urology*, vol. 46, no. 2, pp. 247–253, 2004.

[42] M. Yoshida, Y. Homma, A. Inadome et al., "Age-related changes in cholinergic and purinergic neurotransmission in human isolated bladder smooth muscles," *Experimental Gerontology*, vol. 36, no. 1, pp. 99–109, 2001.

[43] J. Neuhaus, A. Weimann, J. U. Stolzenburg, W. Dawood, T. Schwalenberg, and W. Dorschner, "Histamine receptors in human detrusor smooth muscle cells: physiological properties and immunohistochemical representation of subtypes," *World Journal of Urology*, vol. 24, no. 2, pp. 202–209, 2006.

[44] T. C. Theoharides and G. R. Sant, "Hydroxyzine therapy for interstitial cystitis," *Urology*, vol. 49, no. 5, pp. 108–110, 1997.

[45] P. Dasgupta, S. D. Sharma, C. Womack, H. N. Blackford, and P. Dennis, "Cimetidine in painful bladder syndrome: a histopathological study," *BJU International*, vol. 88, no. 3, pp. 183–186, 2001.

[46] H. Linardou, I. J. Dahabreh, D. Kanaloupiti et al., "Assessment of somatic k-RAS mutations as a mechanism associated with resistance to EGFR-targeted agents: a systematic review and meta-analysis of studies in advanced non-small-cell lung cancer and metastatic colorectal cancer," *The Lancet Oncology*, vol. 9, no. 10, pp. 962–972, 2008.

[47] J. B. Overdevest, D. Theodorescu, and J. K. Lee, "Utilizing the molecular gateway: the path to Personalized cancer management," *Clinical Chemistry*, vol. 55, no. 4, pp. 684–697, 2009.

[48] S. Varambally, J. Yu, B. Laxman et al., "Integrative genomic and proteomic analysis of prostate cancer reveals signatures of metastatic progression," *Cancer Cell*, vol. 8, no. 5, pp. 393–406, 2005.

[49] G. McMurray, N. Dass, and A. F. Brading, "Purinoceptor subtypes mediating contraction and relaxation of marmoset urinary bladder smooth muscle," *British Journal of Pharmacology*, vol. 123, no. 8, pp. 1579–1586, 1998.

[50] K. Fujii, "Evidence for adenosine triphosphate as an excitatory transmitter in guinea-pig, rabbit and pig urinary bladder," *Journal of Physiology*, vol. 404, pp. 39–52, 1988.

[51] A. Apostolidis, P. Dasgupta, and C. J. Fowler, "Proposed mechanism for the efficacy of injected Botulinum toxin in the treatment of human detrusor overactivity," *European Urology*, vol. 49, no. 4, pp. 644–650, 2006.

[52] H. Schulte-Baukloh, J. Neuhaus, K. Miller, and H. H. Knispel, "Botulinum toxin A-harnblaseninjektionen führen zur reduktion muskulärer M2, P2X2 und P2X3-rezeptoren bei kindern und jugendlichen mit neurogener blase," *Urologe*, vol. 49, p. 12, 2010.

[53] T. C. Theoharides, D. Kempuraj, and G. R. Sant, "Mast cell involvement in interstitial cystitis: a review of human and experimental evidence," *Urology*, vol. 57, no. 6, pp. 47–55, 2001.

[54] J. Neuhaus, A. Oberbach, T. Schwalenberg, and J. U. Stolzenburg, "Cultured smooth muscle cells of the human vesical sphincter are more sensitive to histamine than are detrusor smooth muscle cells," *Urology*, vol. 67, no. 5, pp. 1086–1092, 2006.

[55] K. Bouchelouche and P. Bouchelouche, "Cysteinyl leukotriene D4 increases human detrusor muscle responsiveness to histamine," *Journal of Urology*, vol. 176, no. 1, pp. 361–366, 2006.

[56] U. H. Stenman, A. Tiitinen, H. Alfthan, and L. Valmu, "The classification, functions and clinical use of different isoforms of HCG," *Human Reproduction Update*, vol. 12, no. 6, pp. 769–784, 2006.

[57] H. Alexander, C. Biesold, W. Weber, and D. Baier, "[Immunohistochemical evidence of immuno-reactive hCG in the secretory endometrium in women]," *Zentralblatt für Gynäkologie*, vol. 119, supplement 1, pp. 17–22, 1997.

[58] G. Zimmermann, W. Ackermann, and H. Alexander, "Epithelial human chorionic gonadotropin is expressed and produced in human secretory endometrium during the normal menstrual cycle," *Biology of Reproduction*, vol. 80, no. 5, pp. 1053–1065, 2009.

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Review Article

Role of KIT-Positive Interstitial Cells of Cajal in the Urinary Bladder and Possible Therapeutic Target for Overactive Bladder

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In the gastrointestinal tract, interstitial cells of Cajal (ICCs) act as pacemaker cells to generate slow wave activity. Interstitial cells that resemble ICCs in the gastrointestinal tract have been identified by their morphological characteristics in the bladder. KIT is used as an identification marker of ICCs. ICCs in the bladder may be involved in signal transmission between smooth muscle bundles, from efferent nerves to smooth muscles, and from the urothelium to afferent nerves. Recent research has suggested that not only the disturbance of spontaneous contractility caused by altered detrusor ICC signal transduction between nerves and smooth muscle cells but also the disturbance of signal transduction between urothelial cells and sensory nerves via suburothelial ICC may induce overactive bladder (OAB). Recent reports have suggested that KIT is not only a detection marker of these cells, but also may play a crucial role in the control of bladder function. Research into the effect of a c-kit receptor inhibitor, imatinib mesylate, on bladder function implies that KIT-positive ICCs may be therapeutic target cells to reduce bladder overactivity and that the blockage of c-kit receptor may offer a new therapeutic strategy for OAB treatment, although further study will be needed.

1. Introduction

Overactive bladder (OAB) syndrome is characterized by urinary frequency and urgency with or without urge incontinence, and is often accompanied by nocturia. In the USA population, 16.5% (16% of men and 16.9% of women) over 18 years of age had symptoms consistent with OAB [1]. The prevalence of this condition increases with age, and OAB significantly impacts health-related quality of life [1–3].

Urgency is the core symptom of the OAB symptom complex, but the underlying mechanisms are not fully understood [4]. OAB symptoms were traditionally considered to result from overactivity of the bladder detrusor muscle. Drake et al. showed model of peripheral autonomous modules and a myovesical plexus in normal and OAB function, and detrusor overactivity (DO) results from exaggerated symptomatic expression of peripheral autonomous activity, resulting from a shift in the balance of excitation and inhibition in smooth muscle modules [5]. On the other hand, there is increasing evidence showing that the urothelium has specialized sensory and signaling properties, and may mediate urgency [6, 7]. In addition, the role of interstitial cells in mediating urgency and the pathophysiology of OAB has recently attracted considerable attention.

In the gastrointestinal tract, interstitial cells of Cajal (ICC) act as primary pacemaker cells which inject depolarizing currents into neighboring smooth muscles to initiate spontaneous slow waves and corresponding phasic contractions [8], and play a fundamental role in the transmission of signals from enteric neurons to smooth muscle cells [9]. ICCs express the proto-oncogene c-kit, and signaling via the receptor kinase gene product, KIT [10], which is used as an identification marker of ICCs. In the urinary tract, including the renal pelvis, ureter, bladder, and urethra, KIT-positive ICCs, which are referred to as interstitial cells (IC), ICC-like cells, or myofibroblasts [11], have also been identified by their morphological characteristics [5, 12, 13], but show variability among tissues, which may account for individual characteristics of the organs [13].

Many groups have attempted to elucidate their physiological features in the bladder, but have shown that ICC in the bladder does not necessarily have the typical physiological

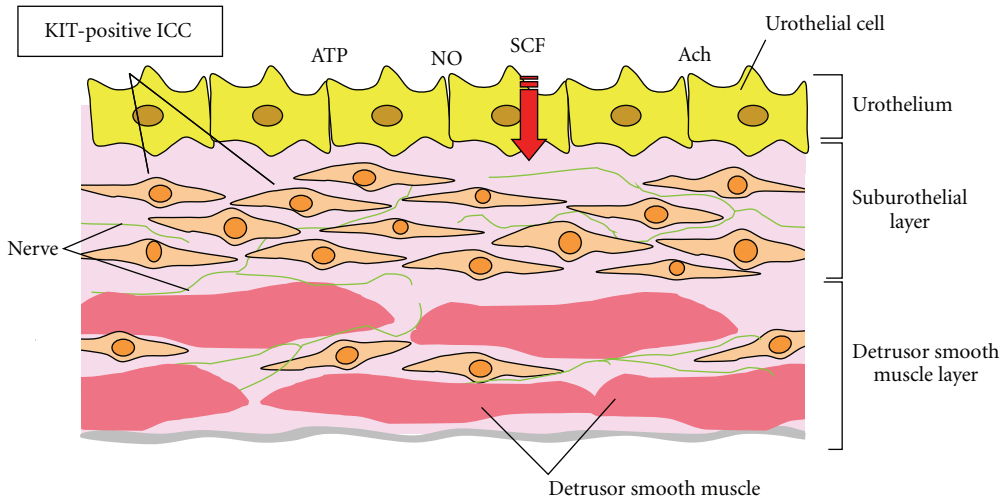


Figure 1: Distribution and morphology of Kit-positive suburothelial and detrusor ICCs and interaction with urothelium, nerves, and smooth muscle.

function of ICC in the gastrointestinal tract [11]. Identifying the functions of ICCs may be a shortcut to clarify the pathophysiology of OAB and DO. Thus, in this review, we summarize the distribution and function of KIT-positive ICC in the bladder as well as the association between KIT-possitive ICCs and OAB, and discuss the possible therapeutic target of KIT-positive ICC for OAB in the future.

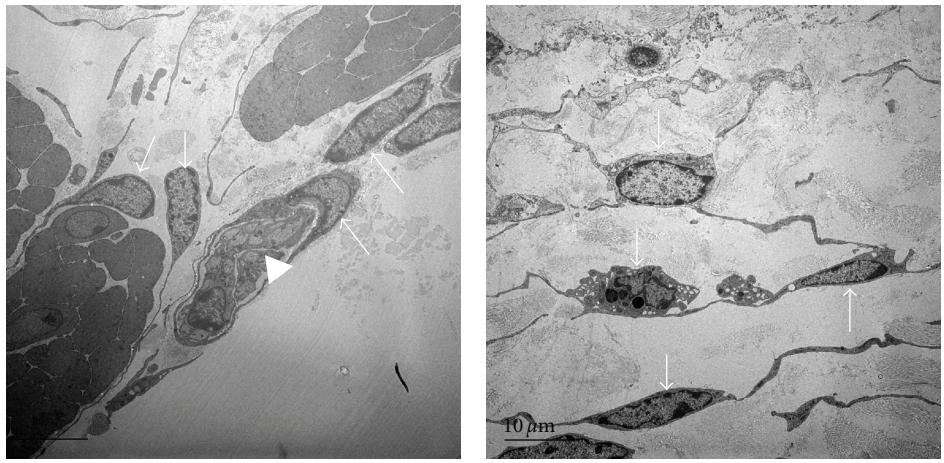
2. Distribution and Morphology of KIT-Positive ICC

ICC has immunoreactivity for vimentin, connexin-43, and cGMP [14–16]. In addition, vanilloid, purinergic, and muscarinic receptors were expressed on suburothelial ICCs [17–19]. On the other hand, KIT, which is expressed by ICC but not smooth muscle or fibroblasts [9, 10], is a well-established detection marker of ICC; however, definitive evidence remains lacking whether KIT was expressed in other structures in the bladder. Some researchers demonstrated that the presence of ICC in the urinary bladder has been demonstrated using antibodies to KIT (also known as c-kit) in rodents and humans. ICCs in the bladder are located throughout the bladder wall [20] and can be divided into at least two subpopulations by their morphology and orientation, that is, ICCs in detrusor smooth muscle layers (detrusor ICCs) and ICCs in the suburothelial layers (suburothelial ICCs) [15, 20, 21]. These ICCs are closely associated with detrusor smooth muscles and make structural interactions with cholinergic nerves in each region [15, 20–22].

In the detrusor smooth muscle layer, ICCs are preferentially located along the boundary of smooth muscle bundles and are also distributed between muscle bundles. They run in parallel with the smooth muscle bundles and are closely associated with intramural nerves [20]. These morphological findings suggest that ICCs in the bladder may act as pacemakers like those in the gastrointestinal tract as well as playing an important role in cell-to-cell communication to integrate signals in the bladder wall, although the hypothesis of the role of ICCs in the urinary bladder as pacemaker cells has remained controversial.

Suburothelial ICCs, which are also referred to as myofibroblasts, have a spindle- and stellate-shaped morphology with several branches emanating from a central soma [11, 20–23]. They are extensively linked by gap junctions to form a functional syncytium [15]. In addition, double-labeling with KIT and a nerve detection marker, PGP9.5, demonstrated that ICCs are in close apposition to one another and nerves, and form a interconnected cellular network [14], supposedly involved in signaling pathways of the bladder, and may play a role in moderating the sensory process, leading to the initiation of the micturition reflex [15] (Figure 1).

ICCs in the bladder were also distinguishable from other cells by their unique ultrastructural features. There are several reports of ultrastructural characterization of ICC observed by transmission electron microscopy [6, 14, 23, 24]. A fundamental feature of ICCs is spindle- or stellate-shaped cells with pale eosinophilic cytoplasm and an elongated electron-dense nucleus (Figure 2). A critical element in the ultrastructure of these cells is the fibronexus, a cell-to-matrix junction, consisting of myofilament and fibronectin filament systems converging on a discrete cell-surface plaque [24]. Rasmussen et al. reported detailed information of the ultrastructure of detrusor ICCs, and revealed two different types of ICC in the human detrusor smooth muscle layer: a CD34-positive, CD-117-negative cell with a slender cytoplasmic process and myoid features, and a fibroblast-like cell. They concluded that detrusor ICCs may be analogous to ICC in the gastrointestinal tract. Wiseman et al. reported the characteristics of suburothelial ICCs [16], showing a layer of cells with the cytological characteristics of both fibroblasts and smooth muscle cells, and that ICCs included bundles of fine cytoplasmic filaments, dense bodies, linear arrays of subsurface vacuoles, and the presence of an interrupted basal lamina. These cells had close contact with unmyelinated axonal varicosities containing a mixture of clear and large



(a) (b)

Figure 2: Electron micrographs of ICC-LC in the guinea-pig bladder. ICC-LCs made close contact with nerves and each other. Arrow: ICC, arrowhead: nerves, ×4,000.

dense-cored vesicles, or clear vesicles alone. Johnston et al. have also shown the ultrastructural profile of ICCs, including an absent thick filament, dense bodies or dense bands typical of smooth muscle cells, and mitochondria, ribosomes, vesicles, Golgi, and a well-developed nondilated rER [23]. These morphological studies provide a basis for future morphological and physiological investigations of ICCs under conditions of impaired bladder function.

3. Function of Kit-Positive ICC

ICCs in the gastrointestinal tract are known to be the origin of pacemaker signals that underlie their spontaneous activity, and they have a major role in the transmission of signals from enteric neurons to smooth muscle cells [25, 26]. Similarly, the bladder develops phasic or autonomous activity consisting of rhythmical transient contractions during the filling phase [27, 28]; however, single myocytes can generate action potentials, but not spontaneously [27]. Hashitani et al. reported that spontaneous action potentials and associated calcium waves occur almost simultaneously along the boundary of bladder smooth muscle bundles and then propagate to the other boundary, probably through gap junctions [29]. Recent evidence suggests that ICCs in the bladder may also play a role in determining the pattern of spontaneous activity, although their precise role is less well established in the urinary tract than in the gastrointestinal tract [30–32]. Therefore, one of the main focuses of some researchers is to identify the role of ICCs as either pacemaker cells to drive the smooth muscle wall or as intermediaries in neuromuscular transmission in the bladder.

Whether ICCs can act as pacemaker cells remains controversial. As described above, in the detrusor muscle layer, ICCs are found preferentially at the boundary of muscle bundles from where spontaneous Ca^{2+} transients originate, suggesting that they may be crucial in generating spontaneous excitation [21]. On the other hand, Hashitani et al. reported that spontaneous Ca^{2+} transients recorded from ICCs in fact occurred independently of those of smooth muscles even when synchronous Ca^{2+} waves swept across muscle bundles [33]. ICCs may be more important in mediating the propagation of action potentials along the bundles than in actually generating them [27, 29]. The finding in the human bladder that c-kit labeling showed significantly more ICCs in human OAB detrusor than in normal specimens [34] may support this suggestion, since in these tissues the contractions appear better coordinated across the strips [20]; therefore, they may not be electrical pacemaker cells.

Recently, it has been suggested that ICCs may function as sensing network receiving/sending signals from/to the urothelium, modulating afferent bladder innervations, and/or activating a spinal or intramural reflex arc [35]. Sui et al. demonstrated that suburothelial ICCs respond to exogenous agents implicated in modulating bladder sensory responses; responses augmented by physical intercellular contact [36]. Not only detrusor ICCs but also suburothelial ICCs show spontaneous electrical and Ca^{2+} signaling [22, 23, 33, 37, 38]. They also respond to exogenous application of neurotransmitters such as adenosine triphosphate (ATP) and acetylcholine (Ach), and express purinergic ($P2Y_6$), cholinergic (M_3) receptors, and prostaglandin receptor types 1 and 2 (EP1 and EP2) [18, 19, 23, 39]. These findings suggest that ICCs act in the sensory processes of the bladder by responding to ATP, Ach, and prostaglandin, and might play an important functional role in the control of bladder function. In addition, other transmitters, such as connexin-43 (gap junctions, e.g., intercellular communication) and cGMP (responds to nitric oxide; NO) expressed by ICCs, are probably very important for normal and pathologic (OAB) physiology [15, 29].

Although KIT is used as an identification marker of ICCs, recent reports have suggested that KIT is not only a detection marker of these cells, but also may play a crucial role in the control of bladder function [34, 40]. Several reports

have evaluated the role of KIT using KIT mutant mice and rats [41–43]. McCloskey et al. have recently reported the physiological function of ICC-like cells in the bladder using heterozygous KIT mutant mice (W/Wv), which have a point mutation at amino acid 660 in *c-kit* that causes a reduction but not abolition of tyrosine kinase activity. These mice had KIT- and vimentin-immunopositive ICC, and there are similarities in the electrical and contractile properties of W/Wv and wildtype detrusors [44]. On the other hand, homozygous KIT mutant WsRC Ws/Ws rats, which have a 12-base deletion in the tyrosine kinase domain of c-kit cDNA rats [41], have impaired pacemaker activity in the ileum and colon, which induced movement disturbance [42, 43]. We investigated morphological and physiological findings in the bladder of KIT mutant rats in order to clarify whether disturbance of the KIT pathways affects bladder activity [45]. Each parameter of cystometry in KIT mutant rats was similar to that of wildtype rats under normal conditions. Interestingly, however, the reduction in intercontraction intervals in KIT mutant rats with chemical cystitis was smaller than in wildtype rats, suggesting reduced noxious bladder sensations in KIT mutant rats. These results indicate that KIT plays an important role in bladder function, especially under pathological conditions, and certain voiding disturbances may be associated with impaired KIT signaling in ICCs.

Stem cell factor (SCF), a natural ligand for KIT, is associated with various biologic phases, such as hematopoiesis, reproduction, regeneration, and cell proliferation [46]; however, the distribution and role of SCF in the urinary bladder remains unknown, although the role of c-kit in the urinary bladder has been gradually clarified. Our preliminary data suggest that SCF produced in the urothelium of the urinary bladder may act as a possible mediator by binding to c-kit [47]. The SCF/c-kit pathway leads to the activation of multiple pathways, including phosphatidyl-inositol-3 kinase, phospholipase C-gamma, Src kinase, Janus kinase/signal transducers, and activators of transcription and mitogen-activated protein kinase pathways [48]. Recognition of the biological properties and elucidation of the mechanism of the SCF/c-kit pathway in the bladder may provide more insight into the physiology of the bladder.

4. KIT-Positive ICC and Pathophysiology of OAB and DO

Human gastrointestinal motility disorders, such as gastroparesis, chronic idiopathic intestinal pseudoobstruction, achalasia, and chronic constipation, have been associated with loss of ICC in dysfunctional regions of the gastrointestinal tract [49]. Although little is known about the role of ICCs in the bladder, the present knowledge suggests that the functions of ICCs may be region-specific, particularly under pathological conditions [50]. There have been reports of the correlation between ICCs in the bladder and OAB or DO. Biers et al. demonstrated that c-kit-positive ICCs are more numerous in human OAB detrusor than normal detrusor [34], suggesting that detrusor ICC is associated with the pathophysiology of OAB. Under OAB conditions, increased electrical coupling between smooth muscle cells may account for enhanced excitability of detrusor smooth muscles [51]. Thus, spontaneous excitation resulting from spontaneous action potentials [52] may spread for a longer distance and cause synchronous contractions of multiple muscle bundles to elevate intravesical pressure [13]. Indeed, micromotions of the bladder wall, which may be attributed to spontaneous contractions of a unit of muscle bundles, have been reported to be enhanced in a rat model of bladder overactivity [53].

Although the urinary bladder urothelium has classically been thought of as a passive barrier, recent studies have demonstrated that the urothelium is involved in sensory mechanisms and releases several bioactive mediators, such as ATP, nitric oxide, and acetylcholine. Although a neurogenic basis has been considered for the changes in both efferent and afferent autonomic nerves, the role of increased signal transmission from the urothelium to afferent nerves via suburothelial ICCs during the micturition reflex has attracted particular considerable attention [54]. Therefore, several researchers have focused on the correlation between suburothelial ICCs and the pathophysiology of OAB and DO, because they may play an important role in signal transmission and be responsible for bladder control. We investigated the distribution of ICCs in guinea-pigs with partial bladder outlet obstruction (PBOO), which showed bladder overactivity in cystometry [55]. The population of KIT or vimentin immunoreactive ICCs was increased in subserosal layers and their distribution was altered in the suburothelial layer in PBOO bladders, suggesting that the altered distribution of ICCs may contribute to the pathophysiology of bladder overactivity. Therefore, not only the disturbance of spontaneous contractility caused by altered ICC signal transduction between nerves and smooth muscle cells in the detrusor smooth muscle layer but also the disturbance of signal transduction between urothelial cells and sensory nerves via suburothelial ICC may induce OAB and DO. In addition, ultrastructural features of ICC changed in the PBOO model. This may produce abnormal signal transduction between ICC and the nerves or smooth muscle cells [55], suggesting that quantitative or qualitative changes in ICCs may account for the pathologically increased signal transmission between either homogenous or heterogeneous populations of cells in the bladder wall; however, since the pathophysiology of human OAB is not necessarily consistent with pBOO-induced detrusor overactivity, further study using human OAB specimens will be needed.

5. KIT-Positive ICC as a Therapeutic Target for OAB in the Future

Normal physiological contraction of the urinary bladder is predominantly mediated by muscarinic receptors, primarily the M_3 subtype, with the M_2 subtype playing a secondary backup role. On the other hand, bladder relaxation seems to be mediated by β-adrenoceptors, in most species involving a strong β_3 component; therefore, interference with the signal transduction of these receptors may be a viable approach to develop drugs for the treatment of OAB [56]. It is

well established that antimuscarinic drugs are effective in reducing symptoms and improving the quality of life of patients with OAB. Currently, antimuscarinic drugs are the first choice in the pharmacological treatment of OAB. Besides their status as the current standard of care, compliance and persistence are often affected by adverse effects. Although selective β_3-adrenoceptor agonists are potentially useful agents for treating OAB, other options of medical treatment for OAB will be needed.

Imatinib mesylate (Glivec) is a selective inhibitor of c-kit receptor tyrosine kinase and the oncogene Bcr-Abl, and has Food and Drug Administration approval for the treatment of chronic myeloid leukemia and gastrointestinal stromal tumor. Several researchers have demonstrated that inhibition of c-kit reduced bladder activity via c-kit receptor on bladder ICCs [15, 34, 35, 40, 57]. We examined the effects of imatinib mesylate on spontaneous excitation and ion channel activity in detrusor smooth muscles of the guinea-pig bladder using intracellular microelectrodes, isometric muscle tension recordings and patch clamp techniques [57]. Imatinib mesylate (10 microM) converted action potential bursts into continuous firing without affecting their shape but at 50 microM abolished spontaneous action potentials in single smooth muscle cells. It had little effect on inward and outward currents at $<10\,\mu$M, but inhibited them at $>50\,\mu$M. We also investigated the effects of imatinib mesylate on intravesical pressure of isolated guinea-pig bladders using whole organ bath techniques, and demonstrated that imatinib mesylate reduced the amplitude of spontaneous pressure rises in the whole bladder in a dose-dependent manner [40]. The results suggest that ICC-like cells may be responsible for generating bursts of action potentials and contractions in detrusor smooth muscle. Biers et al. demonstrated that imatinib mesylate inhibited evoked smooth muscle contraction and spontaneous activity in human OAB detrusor, with less effect on normal human tissue [34]. They also demonstrated that imatinib mesylate improved bladder capacity, compliance, voided volume, urinary frequency and reduced contraction thresholds and spontaneous activity during guinea pig cystometry [34]. Vahabi et al. have recently reported that imatinib mesylate decreased the amplitude and frequency of carbacol-induced phasic contractions in both normal and diabetic tissues in a dose-dependent manner [35]. These reports showed that imatinib mesylate inhibited spontaneous contraction and, as a result, probably reduced OAB symptoms. On the other hand, as described above, bladder suburothelial ICCs may modulate both sensory responses from the bladder wall and spontaneous activity. Sui et al. showed that several responses that influenced bladder activity either directly or through activation of the sensory mechanism were significantly augmented by physical connections between adjacent cells, and such augmentation was abolished by imatinib mesylate [36]. They also found that imatinib mesylate reduced spontaneous contractile activity in the isolated bladder. Although more data about the potential of ICC as target cells will be needed before the clinical implications of these findings are elucidated, KIT-positive ICCs may be one of the therapeutic target cells to reduce bladder overactivity and blocking c-kit receptor may offer a new therapeutic strategy for OAB treatment in the future.

6. Conclusions

The current limitations of improving OAB therapies arise from our lack of knowledge regarding the primary pathophysiology of this disease. Clarifying the role of ICC function in the bladder may lead to greater understanding of the mechanisms of OAB, and provide a novel therapeutic target. KIT-positive ICCs may be involved in signal transmission, between smooth muscle bundles, from efferent nerves to smooth muscles and from urothelium to afferent nerves, and thus could be a crucial target for the pharmacological treatment of OAB and DO in the future; however, since the role of KIT in the urinary bladder is still not fully clarified, further investigation and more evidence will be needed.

Abbreviations

ICC: Interstitial cells of Cajal
OAB: Overactive bladder
DO: Detrusor overactivity
ATP: Adenosine triphosphate
SCF: Stem cell factor.

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References

[1] W. F. Stewart, J. B. Van Rooyen, G. W. Cundiff et al., "Prevalence and burden of overactive bladder in the United States," *World Journal of Urology*, vol. 20, no. 6, pp. 327–336, 2003.

[2] I. Milsom, W. Stewart, and J. Thuroff, "The prevalence of overactive bladder," *American Journal of Managed Care*, vol. 6, no. 11, pp. S565–S573, 2000.

[3] J. N. Liberman, T. L. Hunt, W. F. Stewart et al., "Health-related quality of life among adults with symptoms of overactive bladder: results from a U.S. community-based survey," *Urology*, vol. 57, no. 6, pp. 1044–1050, 2001.

[4] M. C. Michel and C. R. Chapple, "Basic mechanisms of yrgency: preclinical and clinical evidence," *European Urology*, vol. 56, no. 2, pp. 298–308, 2009.

[5] M. J. Drake, I. W. Mills, and J. I. Gillespie, "Model of peripheral autonomous modules and a myovesical plexus in normal and overactive bladder function," *Lancet*, vol. 358, no. 9279, pp. 401–403, 2001.

[6] N. Yoshimura, Y. Kaiho, M. Miyazato et al., "Therapeutic receptor targets for lower urinary tract dysfunction," *Naunyn-Schmiedeberg's Archives of Pharmacology*, vol. 377, no. 4–6, pp. 437–448, 2008.

[7] L. A. Birder and W. C. de Groat, "Mechanisms of disease: involvement of the urothelium in bladder dysfunction," *Nature Clinical Practice Urology*, vol. 4, no. 1, pp. 46–54, 2007.

[8] K. M. Sanders, "A case for interstitial cells of Cajal as pacemakers and mediators of neurotransmission in the gastrointestinal tract," *Gastroenterology*, vol. 111, no. 2, pp. 492–515, 1996.

[9] G. D. S. Hirst and S. M. Ward, "Interstitial cells: involvement in rhythmicity and neural control of gut smooth muscle," *Journal of Physiology*, vol. 550, part 2, pp. 337–346, 2003.

[10] H. Maeda, A. Yamagata, S. Nishlkawa et al., "Requirement of c-kit for development of intestinal pacemaker system," *Development*, vol. 116, no. 2, pp. 369–375, 1992.

[11] K. D. McCloskey, "Interstitial cells in the urinary bladder—localization and function," *Neurourology and Urodynamics*, vol. 29, no. 1, pp. 82–87, 2010.

[12] R. J. Lang, M. A. Tonta, B. Z. Zoltkowski, W. F. Meeker, I. Wendt, and H. C. Parkington, "Pyeloureteric peristalsis: role of atypical smooth muscle cells and interstitial cells of Cajal-like cells as pacemakers," *Journal of Physiology*, vol. 576, part 3, pp. 695–705, 2006.

[13] H. Hashitani, "Interaction between interstitial cells and smooth muscles in the lower urinary tract and penis," *Journal of Physiology*, vol. 576, part 3, pp. 707–714, 2006.

[14] P. J. Smet, J. Jonavicius, V. R. Marshall, and J. de Vente, "Distribution of nitric oxide synthase-immunoreactive nerves and identification of the cellular targets of nitric oxide in guinea-pig and human urinary bladder by cGMP immunohistochemistry," *Neuroscience*, vol. 71, no. 2, pp. 337–348, 1996.

[15] G. P. Sui, S. Rothery, E. Dupont, C. H. Fry, and N. J. Severs, "Gap junctions and connexin expression in human suburothelial interstitial cells," *BJU International*, vol. 90, no. 1, pp. 118–129, 2002.

[16] O. J. Wiseman, C. J. Fowler, and D. N. Landon, "The role of the human bladder lamina propria myofibroblast," *BJU International*, vol. 91, no. 1, pp. 89–93, 2003.

[17] D. Ost, T. Roskams, F. Van Der Aa, and D. De Ridder, "Topography of the vanilloid receptor in the human bladder: more than just the nerve fibers," *Journal of Urology*, vol. 168, no. 1, pp. 293–297, 2002.

[18] G. P. Sui, C. Wu, and C. H. Fry, "Characterization of the purinergic receptor subtype on guinea-pig suburothelial myofibroblasts," *BJU International*, vol. 97, no. 6, pp. 1327–1331, 2006.

[19] S. Grol, P. B. M. Essers, G. A. van Koeveringe, P. Martinez-Martinez, J. de Vente, and J. I. Gillespie, "M3 muscarinic receptor expression on suburothelial interstitial cells," *BJU International*, vol. 104, no. 3, pp. 398–405, 2009.

[20] R. A. Davidson and K. D. McCloskey, "Morphology and localization of interstitial cells in the guinea pig bladder: structural relationships with smooth muscle and neurons," *Journal of Urology*, vol. 173, no. 4, pp. 1385–1390, 2005.

[21] K. D. McCloskey and A. M. Gurney, "Kit positive cells in the guinea pig bladder," *Journal of Urology*, vol. 168, no. 2, pp. 832–836, 2002.

[22] L. Johnston, C. Carson, A. D. Lyons, R. A. Davidson, and K. D. McCloskey, "Cholinergic-induced Ca2+ signaling in interstitial cells of Cajal from the guinea pig bladder," *American Journal of Physiology—Renal Physiology*, vol. 294, no. 3, pp. F645–F655, 2008.

[23] L. Johnston, S. Woolsey, R. M. Cunningham et al., "Morphological expression of KIT positive interstitial cells of Cajal in human bladder," *Journal of Urology*, vol. 184, no. 1, pp. 370–377, 2010.

[24] M. J. Drake, C. H. Fry, and B. Eyden, "Structural characterization of myofibroblasts in the bladder," *BJU International*, vol. 97, no. 1, pp. 29–32, 2006.

[25] S. M. Ward and K. M. Sanders, "Involvement of intramuscular interstitial cells of Cajal in neuroeffector transmission in the gastrointestinal tract," *Journal of Physiology*, vol. 576, no. 3, pp. 675–682, 2006.

[26] K. M. Sanders, S. D. Koh, and S. M. Ward, "Interstitial cells of Cajal as pacemakers in the gastrointestinal tract," *Annual Review of Physiology*, vol. 68, pp. 307–343, 2006.

[27] A. F. Brading, "Spontaneous activity of lower urinary tract smooth muscles: correlation between ion channels and tissue function," *Journal of Physiology*, vol. 570, no. 1, pp. 13–22, 2006.

[28] G. N. Sibley, "A comparison of spontaneous and nerve-mediated activity in bladder muscle from man, pig and rabbit," *Journal of Physiology*, vol. 354, pp. 431–443, 1984.

[29] H. Hashitani, H. Fukuta, H. Takano, M. F. Klemm, and H. Suzuki, "Origin and propagation of spontaneous excitation in smooth muscle of the guinea-pig urinary bladder," *Journal of Physiology*, vol. 530, part 2, pp. 273–286, 2001.

[30] G. P. Sui, C. Wu, N. Severs, D. Newgreen, and C. H. Fry, "The association between T-type Ca2+ current and outward current in isolated human detrusor cells from stable and overactive bladders," *BJU International*, vol. 99, no. 2, pp. 436–441, 2007.

[31] A. Kanai, J. Roppolo, Y. Ikeda et al., "Origin of spontaneous activity in neonatal and adult rat bladders and its enhancement by stretch and muscarinic agonists," *American Journal of Physiology—Renal Physiology*, vol. 292, no. 3, pp. F1065–F1072, 2007.

[32] Y. Ikeda, C. Fry, F. Hayashi, D. Stolz, D. Griffiths, and A. J. Kanai, "Role of gap junctions in spontaneous activity of the rat bladder," *American Journal of Physiology—Renal Physiology*, vol. 293, no. 4, pp. F1018–F1025, 2007.

[33] H. Hashitani, Y. Yanai, and H. Suzuki, "Role of interstitial cells and gap junctions in the transmission of spontaneous Ca2+ signals in detrusor smooth muscles of the guinea-pig urinary bladder," *Journal of Physiology*, vol. 559, part 2, pp. 567–581, 2004.

[34] S. M. Biers, J. M. Reynard, T. Doore, and A. F. Brading, "The functional effects of a c-kit tyrosine inhibitor on guinea-pig and human detrusor," *BJU International*, vol. 97, no. 3, pp. 612–616, 2006.

[35] B. Vahabi, N. G. McKay, K. Lawson, and D. J. Sellers, "The role of c-kit-positive interstitial cells in mediating phasic contractions of bladder strips from streptozotocin-induced diabetic rats," *BJU International*, vol. 107, no. 9, pp. 1480–1487, 2011.

[36] G. P. Sui, C. Wu, A. Roosen, Y. Ikeda, A. J. Kanai, and C. H. Fry, "Modulation of bladder myofibroblast activity: implications for bladder function," *American Journal of Physiology—Renal Physiology*, vol. 295, no. 3, pp. F688–F697, 2008.

[37] G. P. Sui, C. Wu, and C. H. Fry, "Electrical characteristics of suburothelial cells isolated from the human bladder," *Journal of Urology*, vol. 171, no. 2 I, pp. 938–943, 2004.

[38] U. A. Anderson, C. Carson, and K. D. McCloskey, "KCNQ currents and their contribution to resting membrane potential and the excitability of interstitial cells of Cajal from the guinea pig bladder," *Journal of Urology*, vol. 182, no. 1, pp. 330–336, 2009.

[39] M. S. Rahnama'i, G. A. van Koeveringe, P. B. Essers et al., "Prostaglandin receptor EP1 and EP2 site in guinea pig bladder urothelium and lamina propria," *Journal of Urology*, vol. 183, no. 3, pp. 1241–1247, 2010.

[40] Y. Kubota, S. M. Biers, K. Kohri, and A. F. Brading, "Effects of imatinib mesylate (Glivec) as a c-kit tyrosine kinase

inhibitor in the guinea-pig urinary bladder," *Neurourology and Urodynamics*, vol. 25, no. 3, pp. 205–210, 2006.

[41] T. Tsujimura, S. Hirota, S. Nomura et al., "Characterization of Ws mutant allele of rats: a 12-base deletion in tyrosine kinase domain of c-kit gene," *Blood*, vol. 78, no. 8, pp. 1942–1946, 1991.

[42] E. Albertí, H. B. Mikkelsen, X. Y. Wang et al., "Pacemaker activity and inhibitory neurotransmission in the colon of Ws/Ws mutant rats," *American Journal of Physiology—Gastrointestinal and Liver Physiology*, vol. 292, no. 6, pp. G1499–G1510, 2007.

[43] K. Isozaki, S. Hirota, A. Nakama et al., "Disturbed intestinal movement, bile reflux to the stomach, and deficiency of c-kit-expressing cells in Ws/Ws mutant rats," *Gastroenterology*, vol. 109, no. 2, pp. 456–464, 1995.

[44] K. D. McCloskey, U. A. Anderson, R. A. Davidson, Y. R. Bayguinov, K. M. Sanders, and S. M. Ward, "Comparison of mechanical and electrical activity and interstitial cells of Cajal in urinary bladders from wild-type and W/Wv mice," *British Journal of Pharmacology*, vol. 156, no. 2, pp. 273–283, 2009.

[45] S. Okada, Y. Kojima, Y. Kubota, K. Mizuno, S. Sasaki, and K. Kohri, "Attenuation of bladder overactivity in KIT mutant rats," *BJU International*, vol. 108, no. 2b, pp. E97–E103, 2011.

[46] S. Nakagawa and T. Kitoh, "Measurement of KIT ligand/stem cell factor: clinical and biochemical significance," *Current Opinion in Hematology*, vol. 7, no. 3, pp. 133–142, 2000.

[47] Y. Kubota, Y. Kojima, M. Hayase, S. Sasaki, and K. Kohri, "A Kit ligand stem cell factor as a possible mediator inducing overactive bladder," *Journal of Urology*, vol. 183, supplement 4, p. e73, 2010.

[48] L. Reber, C. A. Da Silva, and N. Frossard, "Stem cell factor and its receptor c-Kit as targets for inflammatory diseases," *European Journal of Pharmacology*, vol. 533, no. 1–3, pp. 327–340, 2006.

[49] K. M. Sanders, "Interstitial cells of Cajal at the clinical and scientific interface," *Journal of Physiology*, vol. 576, part 3, pp. 683–687, 2006.

[50] H. Hashitani, "Interaction between interstitial cells and smooth muscles in the lower urinary tract and penis," *Journal of Physiology*, vol. 576, part 3, pp. 707–714, 2006.

[51] A. F. Brading, "A myogenic basis for the overactive bladder," *Urology*, vol. 50, no. 6A, pp. 57–67, 1997.

[52] H. Hashitani, A. F. Brading, and H. Suzuki, "Correlation between spontaneous electrical, calcium and mechanical activity in detrusor smooth muscle of the guinea-pig bladder," *British Journal of Pharmacology*, vol. 141, no. 1, pp. 183–193, 2004.

[53] M. J. Drake, P. Hedlund, I. J. Harvey, R. K. Pandita, K. E. Andersson, and J. I. Gillespie, "Partial outlet obstruction enhances modular autonomous activity in the isolated rat bladder," *Journal of Urology*, vol. 170, no. 1, pp. 276–279, 2003.

[54] W. C. de Groat, "Neurologic basis for the overactive bladder," *Urology*, vol. 50, no. 6A, pp. 36–52, 1997.

[55] Y. Kubota, H. Hashitani, N. Shirasawa et al., "Altered distribution of interstitial cells in the guinea pig bladder following bladder outlet obstruction," *Neurourology and Urodynamics*, vol. 27, no. 4, pp. 330–340, 2008.

[56] E. P. Frazier, S. L. Peters, A. S. Braverman, M. R. Ruggieri, and M. C. Michel, "Signal transduction underlying the control of urinary bladder smooth muscle tone by muscarinic receptors and β-adrenoceptors," *Naunyn-Schmiedeberg's Archives of Pharmacology*, vol. 377, no. 4–6, pp. 449–462, 2008.

[57] Y. Kubota, S. Kajioka, S. M. Biers, E. Yokota, K. Kohri, and A. F. Brading, "Investigation of the effect of the c-kit inhibitor Glivec on isolated guinea-pig detrusor preparations," *Autonomic Neuroscience*, vol. 115, no. 1-2, pp. 64–73, 2004.

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Clinical Study

The Efficacy and Safety of Propiverine Hydrochloride in Patients with Overactive Bladder Symptoms Who Poorly Responded to Previous Anticholinergic Agents

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Objectives. To prospectively examine the efficacy and safety of propiverine hydrochloride in patients with overactive bladder (OAB) symptoms who poorly responded to previous treatment with solifenacin, tolterodine or imidafenacin. *Methods*. Patients aged ≥20 with persisting OAB symptoms (≥6 in OAB symptom score (OABSS)) even after at least 4-week treatment using solifenacin, tolterodine or imidafenacin were enrolled. Propiverine 20 mg/day was administered for 12 weeks to 70 patients who desired the further improvement of OAB symptoms and 3 who had intolerable adverse events of previous drugs. The OABSS and postvoid residual urine volume (PVR) were determined before and at 4 and 12 weeks of treatment. *Results*. Of 73 patients enrolled (29 males and 44 females, median age 71 years), 52 completed the protocol treatment. The OABSS was significantly improved by propiverine treatment (9.0 at baseline, 6.2 at 4 weeks, 6.3 at 12 weeks ($P < 0.001$)). The scores of OAB symptoms (nighttime frequency, urgency and urge incontinence) except daytime frequency also improved significantly. No increase in PVR was observed. The most frequent adverse event was dry mouth (13.7%), followed by constipation (6.8%). *Conclusions*. Propiverine is useful to improve OAB for patients who poorly respond to solifenacin, tolterodine or imidafenacin.

1. Introduction

Overactive bladder (OAB), a syndrome that presents urinary urgency as an essential symptom [1], has a great impact on the quality of life (QOL) of the patient. A nationwide survey conducted in Japan [2] demonstrated that the estimated prevalence of OAB was 12.4% in the general population over age 40. The study showed that 11.2% and 53.0% of subjects with OAB reported "an impact" and "a slight impact" on their QOL by OAB symptoms, respectively, through the impairment of mental health, vitality, physical activity, domestic work, and business work. Since the actual number of patients with OAB has been increasing in parallel with the advancement of aging society, the appropriate treatment strategy should be established immediately.

Drugs with anticholinergic activity are the first-line drugs to treat OAB symptoms [3]. Propiverine hydrochloride is an agent with calcium antagonistic activity in addition to anticholinergic activity [4]. A double-blind randomized control study demonstrated that propiverine was superior to oxybutynin hydrochloride in terms of the improvement of pollakisuria and urinary incontinence associated with neurogenic bladder and unstable bladder [5]. Since its launch in 1993, propiverine hydrochloride has been widely used

in clinical settings in Japan. On the other hand, three new anticholinergic agents, solifenacin succinate, tolterodine tartrate, and imidafenacin, were successively approved and marketed in recent years. Different from propiverine, these drugs have no calcium antagonistic activity. Differences in clinical efficacy remain unknown between propiverine with calcium antagonistic activity and new anticholinergic agents without the activity. In the present study, we examined the clinical efficacy and safety of propiverine for patients with OAB symptoms who poorly responded to previous treatment with solifenacin, tolterodine, or imidafenacin.

2. Methods

The present study was conducted in patients aged ≥20 who had ≥6 points in overactive bladder symptom score (OABSS) [6] even after at least 4-week treatment with solifenacin, tolterodine, or imidafenacin. Of them, 70 patients who desired the further improvement of OAB symptoms and 3 patients who desired to change previous anticholinergic drugs because of their adverse events were enrolled in the study. Propiverine 20 mg q.d. was administered for 12 weeks. Subjective symptoms and objective findings were assessed by the OABSS and determination of PVR, respectively, before and at 4 and 12 weeks of treatment. Information of adverse events reported during the treatment period was collected.

Paired t-test was performed to examine changes in the OBASS and PVR. A combined analysis model was used to investigate differences in therapeutic effects by previous anticholinergic agent and by gender.

The present study was approved by the institutional review board at Sapporo Medical University (no. 19–48) and performed at 19 institutions as a multi-institutional study between January 2008 and December 2009. Written informed consent was obtained from all participants.

3. Results

Twenty-nine men and 44 women were enrolled in the study. Median age of 73 patients was 71 years. No difference was observed in age (mean ± standard deviation) between men (72.6 ± 11.2 years) and women (70.2 ± 11.4 years, $P = 0.38$). Regarding previous anticholinergic agents, 34, 14, and 25 patients received a standard dose of solifenacin, tolterodine, and imidafenacin, respectively. These agents were given for <8 weeks in 22 (30.1%), 8–12 weeks in 11 (15.1%), and ≥12 weeks in 40 (54.8%) patients. Of the 29 men, 15 (51.2%) had received an α1-adrenoceptor antagonist at the entry. The drug was continued without change in the dosage during the study period.

Of 73 subjects, 52 (71.2%) completed the protocol treatment and 21 (28.8%) withdrew from the study. The main reasons of discontinuation were "no visit to the hospital" in 9 and "adverse events" in 7, followed by "withdrawal of the consent" in 2 and deterioration of comorbid diseases in 2.

Of 52 subjects who completed the protocol treatment, the OABSS improved significantly at 4 and 12 weeks of propiverine treatment (Table 1). Among OAB symptoms, nighttime frequency, urgency, and urgency incontinence except daytime frequency showed significant improvements by propiverine treatment. The efficacy of propiverine was analyzed according to previous anticholinergic agent and to gender (Table 2). Regardless of the type of previous anticholinergic agents, the OABSS improved significantly. No significant difference in OABSS change was observed among the previous drugs ($P = 0.31$). Although the OABSS was significantly improved by propiverine treatment in both men and women, propiverine was less effective in men than in women ($P < 0.01$).

Table 1: Changes in overactive bladder symptom scores in 52 patients treated with propiverine hydrochloride.

	Baseline	4 weeks	12 weeks
OABSS	9.0 ± 2.2[(1)]	6.2 ± 3.3**	6.3 ± 3.3**
Daytime frequency	0.9 ± 0.4	0.8 ± 0.6	0.8 ± 0.4
Nighttime frequency	2.3 ± 0.8	1.9 ± 0.8*	1.9 ± 0.9**
Urgency	3.7 ± 0.9	2.3 ± 1.7**	2.2 ± 1.6**
Urgency incontinence	2.2 ± 1.6	1.2 ± 1.6**	1.4 ± 1.6*

OABSS: overactive bladder symptom score.
[(1)]Mean ± standard deviation.
*$P < 0.01$, **$P < 0.001$ (versus baseline, paired t-test).

The effects of propiverine on PVR were analyzed in 50 subjects who completed the protocol treatment and whose PVR was measured. PVRs (mean ± standard deviation) were 31 ± 41, 32 ± 43 ($P = 0.76$), and 32 ± 42 mL ($P = 0.81$) before and at 4 and 12 weeks of treatment, respectively. PVRs did not increase significantly both in men ($n = 19$) and women ($n = 31$) at 4 and 12 weeks of propiverine treatment.

The overall incidence of adverse events was 21.9% (16/73), and all were mild and moderate in intensity (Table 3). Dry mouth was the most frequently reported adverse event in 13.7% (10/73), followed by constipation in 6.8% (5/73). Seven patients discontinued the protocol treatment due to adverse events (dry mouth in 4, urinary retention in 1, gastric distress in 1, and anorexia in 1). Urinary retention was developed in a 70-year-old woman 78 days after administration. All adverse events except anorexia were recovered by discontinuation of the drug.

4. Discussion

Propiverine hydrochloride inhibits abnormal contractions of bladder smooth muscle *in vivo* through not only its anticholinergic activity but also its concurrent calcium antagonistic activity [7]. Calcium antagonistic activity has not been reported with other anticholinergic agents such as solifenacin, tolterodine, and imidafenacin. Although both cholinergic and atropine-resistant contractions are involved in the development of unstable bladder [8], elderly patients with OAB are likely to show the increased involvement of atropine-resistant contractions that poorly respond to anticholinergic agents. Propiverine that significantly inhibits atropine-resistant contractions through the calcium antagonistic activity [9] may be useful for patients with OAB who show the increased involvement of atropine-resistant contractions.

Table 2: Changes in overactive bladder symptoms by previous anticholinergic agent and by gender.

Variables	Overactive bladder symptom scores			P-value[2]
	Baseline	4 weeks	12 weeks	
Solifenacin ($n = 27$)	9.4 ± 2.5[1]	7.2 ± 3.9**	6.5 ± 3.9**	$P = 0.31$
Tolterodine ($n = 10$)	8.4 ± 1.4	4.7 ± 1.7**	5.9 ± 2.5*	
Imidafenacin ($n = 15$)	8.7 ± 2.1	5.4 ± 2.2**	6.1 ± 2.8**	
Male ($n = 21$)	8.5 ± 1.9	6.9 ± 3.2**	6.4 ± 2.9**	$P < 0.01$
Female ($n = 31$)	9.4 ± 2.4	5.7 ± 3.3**	6.1 ± 3.6**	

[1] Mean ± standard deviation.
[2] Comparison among groups (combined analysis model).
*$P < 0.01$, **$P < 0.001$ (versus baseline, paired t-test).

Table 3: Adverse events in 73 patients.

Adverse events	n (%)	Mild	Moderate	Severe	Serious
Dry mouth	10 (13.7)	6	4	0	0
Constipation	5 (6.8)	5	0	0	0
Urinary retention	1 (1.4%)	0	1	0	0
Blurred vision	1 (1.4%)	1	0	0	0
Urinary tract infection	1 (1.4%)	1	0	0	0
Gastric distress	1 (1.4%)	0	1	0	0
Anorexia	1 (1.4%)	0	1	0	0

Mild: no impairment of activity of daily life.
Moderate: limited activity of daily life.
Serve: impossible activity of daily life.
Serious: life-threatening.

In real-world clinical practice, an anticholinergic agent with insufficient efficacy is often switched to another anticholinergic agent. However, this modality has not been clearly proven yet. In the present study, propiverine significantly improved the OABSS in poor responders to previous treatment with solifenacin, tolterodine, or imidafenacin. We speculate that the calcium antagonistic activity which is specific to propiverine allowed the drug to exert efficacy also in patients who had shown the insufficient efficacy of other anticholinergic agents without the activity.

In the present study, a significant gender difference was found in the efficacy of propiverine. Although the reasons why the efficacy of propiverine appeared more rapidly in women than in men remain unknown, differences in the etiology of OAB or pharmacokinetics/pharmacodynamics between men and women may be involved. This is a topic to be investigated in the future because gender difference has never been studied.

Anticholinergic agents are known to develop systemic adverse reactions such as dry mouth, constipation, and impairment of eye accommodation. Propiverine is a drug that is nonselective to muscarinic receptor subtypes. In a treatment outcome survey conducted in approximately 10,000 patients in Japan, the safety of propiverine was verified [10]. Although the incidences of dry mouth and constipation in the present study were 13.7% and 6.8%, respectively, the values were equivalent to those in previous studies.

In the present study, 9 (42.9%) of 21 patients who discontinued the protocol treatment never visited the hospital. The previous survey [10] demonstrated that the major reasons for treatment discontinuation were "symptom improvement" and "no visit to the hospital." Tanaka and Masumori [11] also reported that the improvement of symptoms was a major reason of termination in 21 (68%) of 31 patients who discontinued propiverine treatment. Thus, OAB symptoms were likely to be improved by the short-term intake of propiverine in some patients, which made them never come back to the hospital.

Since this study did not conduct as a double-blind placebo-controlled trial, the placebo effect may be involved in symptomatic improvement. In addition, the improvement may be obtained even by switching among solifenacin, tolterodine, and imidafenacin [12–14]. However, to date, no efficient therapeutic strategy has been established in patients who poorly responded to treatment with anticholinergic agents, because of the lack of well-designed placebo-controlled trials. The observation that propiverine was effective for poor responders to other anticholinergic agents is of great clinical relevance. Therefore, propiverine is considered as one of options for a second-line treatment even if the efficacy of solifenacin, tolterodine, or imidafenacin is insufficient, although the placebo-controlled trial is definitely necessary to prove it.

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References

[1] P. Abrams, L. Cardozo, M. Fall et al., "The standardisation of terminology of lower urinary tract function: report from the standardisation sub-committee of the international continence society," *Neurourology and Urodynamics*, vol. 21, no. 2, pp. 167–178, 2002.

[2] Y. Homma, O. Yamaguchi, and K. Hayashi, "An epidemiological survey of overactive bladder symptoms in Japan," *British Journal of Urology International*, vol. 96, no. 9, pp. 1314–1318, 2005.

[3] O. Yamaguchi, O. Nishizawa, M. Takeda et al., "Clinical guidelines for overactive bladder," *International Journal of Urology*, vol. 16, no. 2, pp. 126–142, 2009.

[4] A. Haruno, Y. Yamasaki, K. Miyoshi et al., "Effects of propiverine and its metabolites on isolated guinea pig urinary bladder," *Folia Pharmacol Japan*, vol. 94, pp. 145–150, 1989.

[5] M. Stohrer, G. Murtz, G. Kramer, F. Schnabel, E. P. Arnold, and J. J. Wyndaele, "Propiverine compared to oxybutynin in neurogenic detrusor overactivity: results of a randomized, double-blind, multicenter clinical study," *European Urology*, vol. 51, no. 1, pp. 235–242, 2007.

[6] Y. Homma, M. Yoshida, N. Seki et al., "Symptom assessment tool for overactive bladder syndrome: overactive bladder symptom score," *Urology*, vol. 68, no. 2, pp. 318–323, 2006.

[7] A. Yamada, Y. Kobayashi, and T. Aita, "Effect of propiverine on the atropine-resistant contraction of urinary bladders in aged rats," *Yamagata Medical Journal*, vol. 26, pp. 53–60, 2008.

[8] K. E. Anderson, "Pharmacology of lower urinary tract smooth muscles and penile erectile tissues," *Pharmacological Reviews*, vol. 45, no. 3, pp. 253–308, 1993.

[9] Y. Sugiyama, M. Yoshida, K. Masunaga et al., "Pharmacological effects of propiverine and its active metabolite, M-1, on isolated human urinary bladder smooth muscle, and on bladder contraction in rats," *International Journal of Urology*, vol. 15, no. 1, pp. 76–81, 2008.

[10] K. Itoh and T. Nishi, "Post marketing surveillance of propiverine hydrochloride (BUP-4 tablets) in pollakiuria and urinary incontinence," *Japanese Pharmacology and Therapeutics*, vol. 30, no. 12, pp. 1023–1036, 2002.

[11] Y. Tanaka and N. Masumori, "Clinical follow-up of patients treated with propiverine hydrochloride for pollakisuria and/or urinary incontinence," *Japanese Journal of Urological Surgery*, vol. 21, pp. 77–80, 2008.

[12] M. B. Chancellor, N. Zinner, K. Whitmore et al., "Efficacy of solifenacin in patients previously treated with tolterodine extended release 4 mg: results of a 12-week, multicenter, open-label, flexible-dose study," *Clinical Therapeutics*, vol. 30, no. 10, pp. 1766–1781, 2008.

[13] S. E. Swift, P. Siami, and S. Forero-Schwanhaeuser, "Diary and patient-reported outcomes in patients with severe overactive bladder switching from tolterodine extended release 4 mg/day to solifenacin treatment: an open-label, flexible-dosing, multicentre study," *Clinical Drug Investigation*, vol. 29, no. 5, pp. 305–316, 2009.

[14] T. Onishi, M. Kato, and A. Hoshina, "The efficacy and safety for switchover treatment with second generation antimuscarinic agent therapy in patients with overactive bladder," *J New Rem Clin*, vol. 59, pp. 374–380, 2010.

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Review Article

Clinical Results of a Brindley Procedure: Sacral Anterior Root Stimulation in Combination with a Rhizotomy of the Dorsal Roots

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The Brindley procedure consists of a stimulator for sacral anterior-root stimulation and a rhizotomy of the dorsal sacral roots to abolish neurogenic detrusor overactivity. Stimulation of the sacral anterior roots enables micturition, defecation, and erections. This overview discusses the technique, selection of patients and clinical results of the Brindley procedure. The Brindley procedure is suitable for a selected group of patients with complete spinal cord injury and detrusor overactivity. Overall, the Brindley procedure shows good clinical results and improves quality of life. However, to remain a valuable treatment option for the future, the technique needs some adequate changes to enable analysis of the implanted parts, to improve revision techniques of the implanted parts, and to abolish the sacral dorsal rhizotomy.

1. Introduction

The Brindley procedure consists of a stimulator for sacral anterior-root stimulation (SARS) and a rhizotomy of the dorsal sacral roots to abolish neurogenic detrusor overactivity. Stimulation of the sacral anterior roots enables micturition, defecation, and erections. The Brindley procedure is suitable for a selected group of skeletally mature patients with complete spinal cord injury and detrusor overactivity, who do not respond adequately to conservative treatments of the detrusor overactivity. Patients with severe autonomic dysreflexia or detrusor-external sphincter dyssynergia will benefit especially from the dorsal rhizotomy. Patients with incomplete injury will lose their sensory function due to the dorsal rhizotomy and have the risk to experience pain sensation during stimulation due to an incomplete rhizotomy. The technique, selection of patients, and clinical results are discussed in this overview.

2. Brindley Stimulator

The Brindley system is composed of an external and implanted part. The implanted part consists of electrodes, connecting cables, and a receiver block. Patients have to position an external stimulating device on the skin over the implanted receiver to evoke stimuli. The receiver does not have a battery. Electrical stimuli are evoked by radiofrequency waves. With the availability of separate stimulation of the sacral levels and various stimulation settings, it is possible to set various stimulation programs to optimize micturition, defecation, and penile erections.

A tripolar electrode cuff is used for intradural stimulation of the sacral anterior roots. A three-channel implant is composed of two books. The upper book contains three parallel slots for S3 (one slot) and S2 roots (two slots at one channel), and the lower contains one slot for S4 roots. Each slot contains one cathode in the centre and an anode at each of the two ends to avoid stimulation of tissue structures outside the slot. The two-channel implant allows stimulation of two root levels or sets of root levels. The four-channel implant has the same configuration as the three-channel implant but allows independent stimulation of four sets of roots. The choice for the number of channels depends on the number of different rootlet combinations that have to be stimulated. Each channel is connected to the subcutaneous receiver block by a silicone-coated cable.

Extradural electrodes are used in patients in whom intradural electrodes could not be placed due to, for example, arachnoiditis or a previous intradural electrode implantation that failed. Some centres prefer to use extradural electrodes primarily for nearly all patients. The extradural implant has three helical electrodes at its end, which are also configured with a cathode between two anodes.

3. Poststimulus Voiding

Most of the small diameter parasympathetic efferent nerve fibres for innervation of the bladder are located in the sacral anterior roots (S2–S4/5). Small-diameter nerve fibres need a higher stimulus for their excitation than large-diameter fibres. Consequently, electrical stimulation of the anterior roots for detrusor contractions also causes contraction of the urethral sphincter due to stimulation of somatic large-diameter nerve fibres. This prevents emptying of the bladder. To overcome this problem, poststimulus voiding is used. The time to relax of striated muscles of the urethral sphincter is shorter than the relaxation time of smooth muscles of the detrusor. When intermittent stimulation pulse trains are applied, the difference in muscle relaxation time can be used to achieve a sustained detrusor muscle contraction with intervals of urethral sphincter relaxation (Figure 1). These intervals in between stimulations allow a decrease of the urethral sphincter pressure while a high intravesical pressure remains. This results in poststimulus voiding with an intermittent pattern of the micturition flow. A comparable mechanism has been used for defecation.

4. Dorsal Rhizotomy of the Sacral Nerves

Sauerwein structurally expanded SARS with a dorsal rhizotomy (deafferentation) of sacral roots S2 till S5 [1]. A dorsal rhizotomy is important because it suppresses neurogenic detrusor overactivity and detrusor-external sphincter dyssynergia [1, 2]. This results in a low-pressure bladder without reflex contractions of the detrusor and subsequently continence. Moreover, it reduces autonomic dysreflexia [2, 3]. Therefore, a dorsal rhizotomy can also be applied in combination with intermittent catheterization to empty the bladder without implantation of a Brindley stimulator [3].

5. Patient Selection

Patients need to have intact efferent nerve pathways to the bladder and a bladder that is able to contract. Contractions of at least 50 cm H_2O in males or 30 cm H_2O in females need to be present during filling cystometry [4]. If no sufficient spontaneous contraction occurs, suitable patients can be selected by rectal stimulation according to electroejaculation procedures or direct needle stimulation of the sacral roots to provoke bladder contractions.

Preoperative magnetic resonance imaging is used to exclude arachnoiditis at the level of the conus and cauda equine or other neurological disorder of the spinal cord. Patients with active or previous arachnoiditis are not suitable for intradural electrode implantation.

6. Implantation

A laminectomy from L3-L4 to S1-S2 is done for an intradural rhizotomy and intradural implantation of the electrode cuff. The dura and arachnoid are opened at midline to expose the sacral nerve roots. The anterior and dorsal components of the roots, especially relevant anterior roots for micturition, can be identified intradurally by electrical stimulation of these components while monitoring the effects on detrusor activity, blood pressure, and somatomotor responses. A rhizotomy of the identified dorsal sacral roots is done. The anterior sacral roots are positioned into the electrode cuff. The connecting cables are subcutaneously tunnelled to a subcutaneous pocket for the receiver.

Implantation of extradural electrodes requires a laminectomy from L5-S1 to S3-S4. The dorsal rhizotomy is done at the level of the ganglia of S2-S5. Electrical stimulation tests are used to identify the anterior and dorsal components of the sacral roots. The extradural electrode is implanted and fixated to the nerve using a strip of silicone rubber sheet which is sewn to itself and surrounds the nerve. The connecting cables and the receiver are implanted the same way as the intradural procedure.

7. Clinical Results

Table 1 shows an overview of publications on the clinical results of the Brindley procedure [3–20]. These results comprise both the Brindley stimulator, which enables stimulation for micturition, defecation, and erections, and the dorsal rhizotomy to achieve continence. The use of the Brindley procedure for micturition and defecation, and the ability to evoke erections are summarised in Figure 2, including urinary continence rates. No accumulation of results is possible due to the overlap of results of several reports, especially the multicentre reports.

The Brindley stimulator is used for micturition in 73% to 100% of patients during followup. These are considerable percentages, but it should be noted that this includes patients who use additional methods to empty their bladder. Additional methods comprise intermittent catheterization, abdominal straining (Valsalva manoeuvre), abdominal compression (Credé manoeuvre), or suprapubic tapping for reflex contractions. Stimulation that is not always completely successful can be found back in the percentages of patients that have less than 50 mL residual urine after stimulation for micturition. These percentages are lower than the percentages of patients that use the stimulator for micturition. Overall, the percentages of patients having urinary tract infections and the frequency of urinary tract infections decrease after the Brindley procedure compared to the preoperative treatment.

The Brindley stimulator is used for defecation in 29% to 100% of patients in different degrees. Not all patients achieve complete evacuation of defecation using only stimulation.

Table 1: Publications on clinical results of the Brindley procedure.

Author	Patients in followup	Rhizotomy (intradural/ extradural)	Implantation (intradural/ extradural)	Followup (years)	Autonomic dysreflexia (before/after)	Use for voiding (% of patients)	Continence (% of patients)	Bladder capacity (% of increase)	Residual urine (% of patients)	UTI incidence (% of patients or incidence/year)	Use for defecation (% of patients)	Use for erections (% of males)
Brindley et al. [4]	38 ♂ 12 ♀	17/0 (S2 and/or S3)	50/0	1–9	0/1 (during stimulation)	86%	62%	—	80% <60 mL	—	—	68%
Madersbacher et al. [12]	1 ♂ 6 ♀	7/0	7/0	—	—(1 during stimulation)	100%	100%	122%	100% <40 mL	After 0%	29%	100%
Robinson et al. [14]	20 ♂ 2 ♀	—	—	—	—	73%	68%	—	—	—	—	30% (0% of ♂ used stimulation for sexual intercourse)
MacDonagh et al. [11]	9 ♂ 3 ♀	9/0	12/0	2.2	—	100%	—	—	—	—	50% complete emptying with stimulation	—
Sauerwein et al. [16]	5 ♂ 6 ♀	0/12	0/12	—	—	82%	64%	—	100% <50 mL	—	—	—
Van Kerrebroeck et al. [19]	90 ♂ 94 ♀ ∗∗	—	166/18	—	26/10	92%	86%	—	82% < 30 mL	Before 88% After 17%	70%	74% (32% of ♂ used stimulation for sexual intercourse)
Madersbacher et al. [13]	8 ♂ 22 ♀	—	27/4	—	—	97%	93%	—	90% <50 mL	—	—	—
Sarrias et al. [15]	1 ♂ 6 ♀	7/0	0/7	—	—	100%	100%	—	100% <50 mL	—	100%	—
Brindley [6]	271 ♂ 229 ♀ ∗∗	—	≤477/≥23	4	—(3 during stimulation)	86%	—	—	—	—	—	—

Table 1: Continued.

Author	Patients in followup	Rhizotomy (intradural/ extradural)	Implantation (intradural/ extradural)	Followup (years)	Autonomic dysreflexia (before/after)	Use for voiding (% of patients)	Continence (% of patients)	Bladder capacity (% of increase)	Residual urine (% of patients)	UTI incidence (% of patients or incidence/year)	Use for defecation (% of patients)	Use for erections (% of males)
Van Kerrebroeck et al. [3]	29 ♂ 18 ♀	47/0	47/0	3.5	7/5 (2 during stimulation)	96%	91%	—	87% < 50 mL	Before 4.2/year After 1.4/year	87%	62% (21% of ♂ used stimulation for sexual intercourse)
Schurch et al. [17]	3 ♂ 7 ♀	10/0	10/0	3.4	6/6 (during stimulation)	100%	80%	213%	100% <50 mL	Before 80% After 60%	—	—
Egon et al. [8]	68 ♂ 28 ♀	−/−	90/9	5.4 ♂ 5.8 ♀	22/0	90%	89%	134% ♂ 375% ♀ (range 300–600)	86% <50 mL	Before 100% After 31%	55% (41% of these complete evacuation with stimulation alone)	75% (26% of ♂ used stimulation for sexual intercourse)
V/d Aa et al. [18]	33 ♂ 4 ♀	37/0	37/0	0.3–12	—	100%	84%	—	73% <30 mL	—	73%	88%
Bauchet et al. [5]	6 ♂ 14 ♀	20/0	20/1	4.5	3/0	90%	90%	142%	95% <50 mL	—	40%	—
Creasey et al. [7]	16 ♂ 7 ♀	23/0	0/23	>1	8/2	78%	87%	—	70% <50 mL	Before 3/year After 2/year	100%	—
Vastenholt et al. [20]	32 ♂ 5 ♀	37/0	37/0	7.2	—	87%	57%	—	—	—	60%	65% (0% of ♂ used stimulation for sexual intercourse)
Hamel et al. [9]	4 ♂	4/0	0/4	—	—	100%	75%	—	100% <50 mL	—	50%	75% (0% of ♂ used stimulation for sexual intercourse)
Kutzenberger et al. [10]	440 ♂+♀	Almost all intradural	Almost all intradural	6.6	187/2	95%	83%	172%	—	Before 6.3/year After 1.2/year	91%	—

This overview includes several multicentre studies (∗∗) which include overlapping results with the reports of various single centre studies. Therefore, no accumulation of results is possible.
(−), unreported data or incomplete data for calculation; UTI, urinary tract infection.

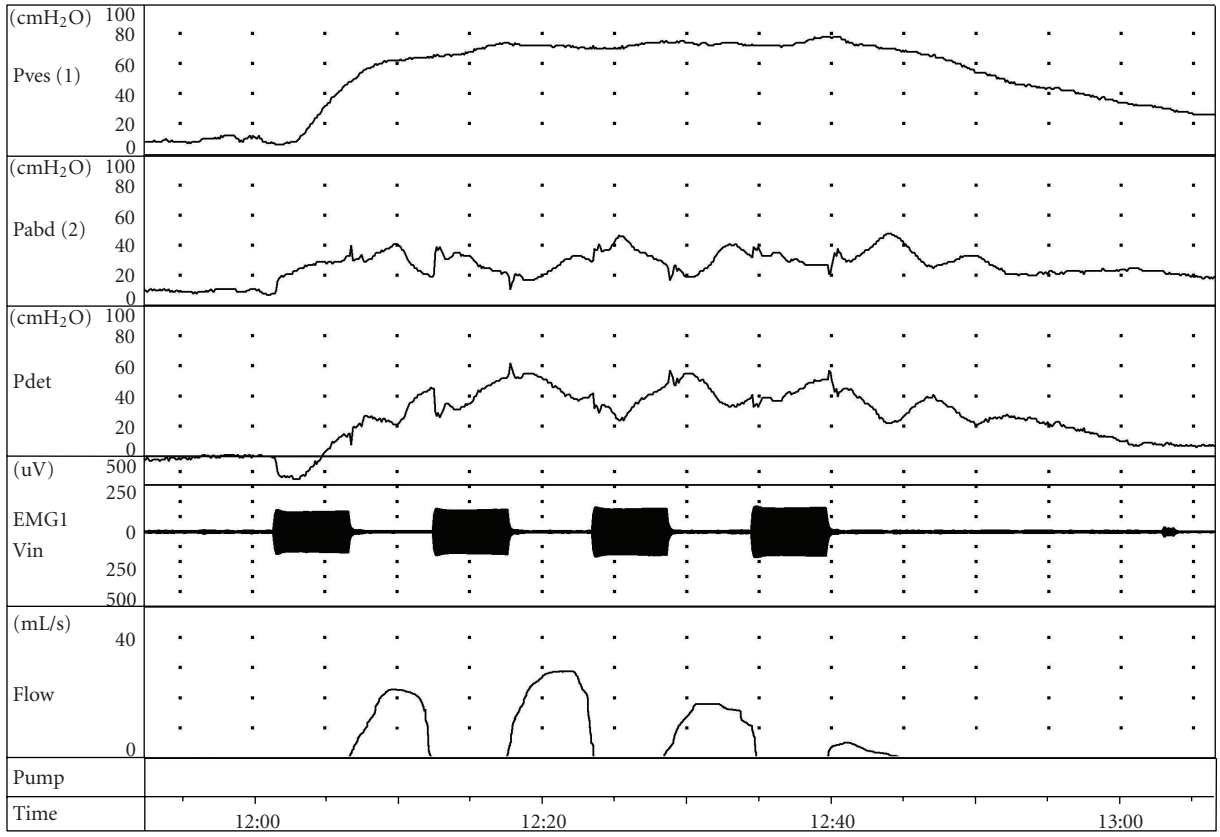

Figure 1: Example of poststimulus voiding using a Brindley stimulator. The three upper traces show the intravesical (Pves), intra-abdominal (Pabd), and detrusor (Pdet) pressures during stimulation with a Brindley stimulator. The increase in EMG signal reflects the activation of the stimulus during 5 seconds. Stimulation is activated every 12 seconds. The intermittent stimulation pattern allows the urethral sphincter to relax while the detrusor pressure remains elevated. This results in an intermittent flow pattern.

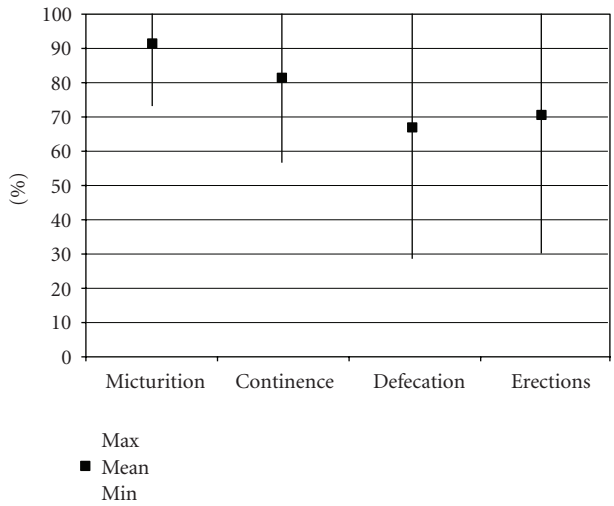

Figure 2: Results of the Brindley procedure on micturition, continence, defecation, and erections are summarised.

Some patients need laxatives in addition to prevent constipation or enable defecation. Many patients only use the stimulator to get the defecation into the rectum, to enable digital evacuation.

Erections can be evoked in a substantial number of patients, but results vary considerably. This can be explained by the relatively low number of patients that actually use the stimulator to evoke erections for sexual intercourse (0–32%), due to qualitatively inadequate erections for sexual intercourse or deterioration of the stimulation effect over time.

Autonomic dysreflexia mostly decreased after the Brindley procedure as a result of the dorsal rhizotomy. Only a few studies reported stimulation-induced autonomic dysreflexia.

Continence is achieved in 57% to 100% of patients, and bladder capacity increased. However, continence is not only achieved by a dorsal rhizotomy. Results on continence also included additional treatments, like anticholinergics and stress incontinence surgery.

8. Discussion

The ultimate treatment of neurogenic disorders of the lower urinary tract would be resolvement of the neurogenic disorder that causes the bladder problems to restore the innervation of the bladder. As long as this causal treatment is not available, symptomatic treatment options are required.

Intravesical Botulinum toxin A injections are an evolving option in the current treatment arsenal. At the time when this paper was written, approval for urological application was expected within short time. However, the Brindley procedure has several advantages for suitable patients compared to Botulinum toxin A in combination with intermittent catheterization, especially if not only the urological properties of the treatments are taken into account. Spinal cord injury comprises a variety of coherent, physical problems. Therefore, management of multiple organ dysfunctions should be advocated. The Brindley procedure does not only enable continence and micturition, but also complete defecation or improvement of defecation pattern, penile erections, and reduction of autonomic dysreflexia and spasms. Patients become less dependent because they do not need assistance for intermittent catheterization anymore and can empty their bladder whereever and whenever. When the treatment options are discussed with a patient, this more extensive application of the Brindley procedure should be mentioned.

The Brindley procedure generally shows good clinical results for restoration of function in spinal cord injury patients with multiple organ dysfunction, including bladder, bowel, and erectile dysfunction. Moreover, the Brindley procedure improves quality of life [20, 21]. However, it is not a procedure that is easy to apply in clinical practice. Firstly, not every patient is suited for the procedure and the success depends on selection of appropriate patients. Prerequisites are a complete spinal cord lesion since neurostimulation can cause pain in incomplete spinal cord lesions, an intact sacral motor neuron pathway enabling stimulation of the bladder, and a detrusor muscle that is capable to contract on stimulation. Secondly, a dorsal rhizotomy and implantation of a Brindley stimulator is complex and not a routine procedure for urologists and should be reserved for specialized centres. Thirdly, the technique is also prone to failures, including the external and implanted components. Analysis of the external components is easy to apply. Currently, a straightforward solution for analysis and revision of the implanted system without major surgery is not available in every country. This can be explained by national legislation with respect to certain aspects of the surgical procedure for revision of the implant, like burning the insulation of the implanted electrode cables. This excludes these patients from the thorough analysis of the implanted components and revision surgery to restore function of their stimulator. Nowadays, most patients have become increasingly familiar with intermittent catheterization and bowel rinsing. They accept the dysfunction of the stimulator more frequently because they remain continent due to their dorsal rhizotomy in combination with controlled emptying of their bladder and bowels.

A main issue for patients who consider a Brindley procedure is the irreversibility of the rhizotomy, and the possibility that future treatment options are not within reach anymore. Although SARS can restore penile erections after a rhizotomy, qualitative useful stimulation of erections is not possible in a substantial number of patients. Therefore, the dorsal rhizotomy should be replaced by a less invasive procedure to abolish detrusor overactivity. Continuous or conditional neuromodulation could be one of the solutions [22, 23]. Sacral posterior- and anterior- root stimulation combines neuromodulation and SARS without a rhizotomy of the dorsal roots for micturition. These new developments are, however, not generally introduced as a standard treatment. Sacral posterior and anterior root stimulation effectively suppress DO but do not result in complete emptying in all patients due to persisting detrusor-external sphincter dyssynergia [24]. This requires development of techniques that prevent backward stimulation when the anterior roots are stimulated to enable selective detrusor stimulation, like selective anodal block and high-frequency block [25–28].

9. Conclusion

The Brindley procedure shows good clinical results and improves quality of life. However, to remain a valuable treatment option for the future, the technique needs some adequate changes to enable analysis of the implanted parts, to improve revision techniques of the implanted parts, and to abolish the sacral dorsal rhizotomy.

References

[1] D. Sauerwein, "Surgical treatment of spastic bladder paralysis in paraplegic patients. Sacral deafferentation with implantation of a sacral anterior root stimulator," *Urologe A*, vol. 29, no. 4, pp. 196–203, 1990.

[2] M. Hohenfellner, J. Pannek, U. Bötel et al., "Sacral bladder denervation for treatment of detrusor hyperreflexia and autonomic dysreflexia," *Urology*, vol. 58, no. 1, pp. 28–32, 2001.

[3] P. E. V. Van Kerrebroeck, E. L. Koldewijn, P. F. Rosier, H. Wijkstra, and F. M. J. Debruyne, "Results of the treatment of neurogenic bladder dysfunction in spinal cord injury by sacral posterior root rhizotomy and anterior sacral root stimulation," *Journal of Urology*, vol. 155, no. 4, pp. 1378–1381, 1996.

[4] G. S. Brindley, C. E. Polkey, D. N. Rushton, and L. Cardozo, "Sacral anterior root stimulators for bladder control in paraplegia: the first 50 cases," *Journal of Neurology Neurosurgery and Psychiatry*, vol. 49, no. 10, pp. 1104–1114, 1986.

[5] L. Bauchet, F. Segnarbieux, G. Martinazzo, P. Frerebeau, and F. Ohanna, "Neurosurgical treatment of hyperactive bladder in spinal cord injury patients," *La Neurochirurgie*, vol. 47, no. 1, pp. 13–24, 2001.

[6] G. S. Brindley, "The first 500 patients with sacral anterior root stimulator implants: general description," *Paraplegia*, vol. 32, no. 12, pp. 795–805, 1994.

[7] G. H. Creasey, J. H. Grill, M. Korsten et al., "An implantable neuroprosthesis for restoring bladder and bowel control to patients with spinal cord injuries: a multicenter trial," *Archives of Physical Medicine and Rehabilitation*, vol. 82, no. 11, pp. 1512–1519, 2001.

[8] G. Egon, M. Barat, P. Colombel, C. Visentin, J. L. Isambert, and J. Guerin, "Implantation of anterior sacral root stimulators combined with posterior sacral rhizotomy in spinal injury patients," *World Journal of Urology*, vol. 16, no. 5, pp. 342–349, 1998.

[9] O. Hamel, B. Perrouin-Verbe, and R. Robert, "Brindley technique with intradural deafferentation and extradural implantation by a single sacral laminectomy," *La Neurochirurgie*, vol. 50, no. 6, pp. 661–666, 2004.

[10] J. Kutzenberger, B. Domurath, and D. Sauerwein, "Spastic bladder and spinal cord injury: seventeen years of experience with sacral deafferentation and implantation of an anterior root stimulator," *Artificial Organs*, vol. 29, no. 3, pp. 239–241, 2005.

[11] R. P. Macdonagh, W. M. Sun, R. Smallwood, D. Forster, and N. W. Read, "Control of defecation in patients with spinal injuries by stimulation of sacral anterior nerve roots," *British Medical Journal*, vol. 300, no. 6738, pp. 1494–1497, 1990.

[12] H. Madersbacher, J. Fischer, and A. Ebner, "sacral root stimulator (Brindley): experiences especially in women with neurogenic urinary incontinence," *Neurourology and Urodynamics*, vol. 7, no. 6, pp. 593–601, 1988.

[13] H. Madersbacher and J. Fischer, "Sacral anterior root stimulation: prerequisites and indications," *Neurourology and Urodynamics*, vol. 12, no. 5, pp. 489–494, 1993.

[14] L. Q. Robinson, A. Grant, P. Weston, T. P. Stephenson, M. Lucas, and D. G. Thomas, "Experience with the Brindley anterior sacral root stimulator," *British Journal of Urology*, vol. 62, no. 6, pp. 553–557, 1988.

[15] M. Sarrias, F. Sarrias, and A. Borau, "The "Barcelona" technique," *Neurourology and Urodynamics*, vol. 12, no. 5, pp. 495–496, 1993.

[16] D. Sauerwein, W. Ingunza, J. Fischer et al., "Extradural implantation of sacral anterior root stimulators," *Journal of Neurology Neurosurgery and Psychiatry*, vol. 53, no. 8, pp. 681–684, 1990.

[17] B. Schurch, B. Rodic, and D. Jeanmonod, "Posterior sacral rhizotomy and intradural anterior sacral root stimulation for treatment of the spastic bladder in spinal cord injured patients," *Journal of Urology*, vol. 157, no. 2, pp. 610–614, 1997.

[18] H. E. van der Aa, E. Alleman, A. Nene, and G. Snoek, "Sacral anterior root stimulation for bladder control: clinical results," *Archives of Physiology and Biochemistry*, vol. 107, no. 3, pp. 248–256, 1999.

[19] P. E. Van Kerrebroeck, E. L. Koldewijn, and F. M. Debruyne, "Worldwide experience with the Finetech-Brindley sacral anterior root stimulator," *Neurourology and Urodynamics*, vol. 12, no. 5, pp. 497–503, 1993.

[20] J. M. Vastenholt, G. J. Snoek, H. P. J. Buschman, H. E. Van Der Aa, E. R. J. Alleman, and M. J. Ijzerman, "A 7-year follow-up of sacral anterior root stimulation for bladder control in patients with a spinal cord injury: quality of life and users' experiences," *Spinal Cord*, vol. 41, no. 7, pp. 397–402, 2003.

[21] F. M. Martens, P. P. den Hollander, G. J. Snoek, E. L. Koldewijn, P. E. van Kerrebroeck, and J. P. Heesakkers, "Quality of life in complete spinal cord injury patients with a Brindley bladder stimulator compared to a matched control group," *Neurourology and Urodynamics*, vol. 30, no. 4, pp. 551–555, 2011.

[22] J. Hansen, S. Media, M. Nøhr, F. Biering-Sørensen, T. Sinkjaer, and N. J. M. Rijkhoff, "Treatment of neurogenic detrusor overactivity in spinal cord injured patients by conditional electrical stimulation," *Journal of Urology*, vol. 173, no. 6, pp. 2035–2039, 2005.

[23] A. P. S. Kirkham, N. C. Shah, S. L. Knight, P. J. R. Shah, and M. D. Craggs, "The acute effects of continuous and conditional neuromodulation on the bladder in spinal cord injury," *Spinal Cord*, vol. 39, no. 8, pp. 420–428, 2001.

[24] A. P. S. Kirkham, S. L. Knight, M. D. Craggs, A. T. M. Casey, and P. J. R. Shah, "Neuromodulation through sacral nerve roots 2 to 4 with a Finetech-Brindley sacral posterior and anterior root stimulator," *Spinal Cord*, vol. 40, no. 6, pp. 272–281, 2002.

[25] A. Boger, N. Bhadra, and K. J. Gustafson, "Bladder voiding by combined high frequency electrical pudendal nerve block and sacral root stimulation," *Neurourology and Urodynamics*, vol. 27, no. 5, pp. 435–439, 2008.

[26] G. S. Brindley and M. D. Craggs, "A technique for anodally blocking large nerve fibres through chronically implanted electrodes," *Journal of Neurology Neurosurgery and Psychiatry*, vol. 43, no. 12, pp. 1083–1090, 1980.

[27] N. J. Rijkhoff, H. Wijkstra, P. E. Van Kerrebroeck, and F. M. Debruyne, "Selective detrusor activation by electrical sacral nerve root stimulation in spinal cord injury," *The Journal of Urology*, vol. 157, no. 4, pp. 1504–1508, 1997.

[28] C. Seif, P. M. Braun, S. Bross et al., "Selective block of urethral sphincter contraction using a modified brindley electrode in sacral anterior root stimulation of the dog," *Neurourology and Urodynamics*, vol. 21, no. 5, pp. 502–510, 2002.

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Review Article

An Overview of the Clinical Use of Antimuscarinics in the Treatment of Overactive Bladder

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Overactive bladder is a common and bothersome condition. Antimuscarinic agents, as a class, are the cornerstone of medical treatment of overactive bladder. They offer significant improvements in symptoms and patients' quality of life. Antimuscarinics are generally well tolerated with mild and predictable side effects. Available antimuscarinics have small, yet statistically significant, differences in their efficacy and tolerability profiles. In clinical practice, finding the agent that offers the optimum balance of efficacy and side effects for an individual patient remains the major challenge.

1. Introduction

Overactive bladder (OAB) is a lower urinary tract condition, characterized by symptoms of urgency, with or without urge incontinence, usually with frequency and nocturia. This symptom complex significantly affects patient's quality of life. In most cases, the underlying pathophysiology is an involuntary detrusor contraction during the storage phase of the voiding cycle [1].

Normal bladder contraction during voiding involves stimulation of the muscarinic receptors on the detrusor muscle by acetylcholine (Ach). The role of Ach in the pathogenesis of involuntary contractions during the storage phase is elusive. Despite the fact that detrusor may contract spontaneously, as a result of the intrinsic activity of the myocyte or of small units of smooth muscle cells [2], Ach is still released from the nerves or from nonneurogenic sources, like the urothelium. A direct or indirect effect of Ach should be considered [2]. Muscarinic receptors are also found on the presynaptic nerve terminals to the bladder participating in the regulation of transmitter release. Currently, there is increasing evidence for an important role of afferent pathways in the pathophysiology of involuntary detrusor contractions [2, 3]. Antimuscarinics, which block muscarinic receptors, have been the treatment of choice for overactive bladder for decades. They affect the efferent control on detrusor contraction, but increasing evidence also suggests a role in afferent pathways' regulation.

There are several subtypes of muscarinic receptors. The human detrusor contains mainly the M_2 and M_3 subtypes [4]. Available antimuscarinics vary in their selectivity for muscarinic receptors.

Oxybutynin [5–8], Tolterodine [9], propiverine [10], solifenacin [11, 12], darifenacin [13, 14], trospium [15, 16], and fesoterodine [17] are antimuscarinic agents approved for use in OAB treatment. Evidence on the efficacy and safety of these agents as a class is reviewed here, and issues concerning their clinical application are discussed.

2. Materials and Methods

The current literature on the efficacy and safety of antimuscarinics was reviewed by searching Medline/PubMed for relevant articles, published in English between 1980 and 2010.

3. Results and Discussion

3.1. Antimuscarinics

3.1.1. Oxybutynin. Oxybutynin is the first antimuscarinic used for the treatment of OAB. In addition to its

antimuscarinic action, oxybutynin in high doses exerts muscle-relaxant and local anaesthetic effects [5–8].

Oxybutynin is now available in oral, immediate (IR) and extended release (ER), as well as two transdermal formulations, a patch and a gel. An intravesical formulation of oxybutynin has also been studied [18].

Oxybutynin IR formulation was the fist that entered clinical practice. Despite its satisfactory efficacy, the substantial incidence of dry mouth, immediate release oxybutynin's most common and bothersome side-effect, limited its tolerability. Newer formulations aimed at eliminating peaks in concentration of oxybutynin and its metabolites in order to reduce related side effects.

The ER formulation of oxybutynin provides a smooth plasma concentration profile over the 24-hour dosage interval, facilitating once-daily administration. Hence, given its overall efficacy/tolerability and dose flexibility, oxybutynin ER provides an alternative in the first line of pharmacotherapy for OAB [8]. Overall, as shown in the OPERA study [19], oxybutynin ER has modestly greater efficacy than tolterodine ER at its most commonly prescribed dose. In the OBJECT study, oxybutynin ER was more effective than tolterodine IR at the endpoints of urge incontinence, total incontinence, and micturition frequency episodes [20].

The transdermal oxybutynin (OXY-TDS) formulation offers patients with urinary incontinence an effective, safe and well-tolerated option for managing the symptoms of overactive bladder [7, 21]. As OAB contributes to decreased work productivity due to job interruptions as well as fatigue, the use of OXY-TDS may result in productivity improvement when patients receive 3.9 mg/day via twice weekly patch application for up to 6 months [22].

Oxybutynin chloride topical gel (OTG) was approved in January 2009 by the US FDA. OTG was designed to provide steady plasma oxybutynin levels with daily application, favorably altering the circulating N-desethyloxybutynin metabolite to oxybutynin ratio, thus minimizing the antimuscarinic adverse effects of oral formulations. The use of a biocompatible delivery system also reduced the application-site skin reactions associated with other available forms of transdermal delivery. OTG represents an efficacious, safe, and convenient alternative to other oxybutynin formulations and oral antimuscarinics for the treatment of OAB [23].

Interestingly, all the above-mentioned oxybutynin formulations have been shown to be more efficacious than the IR oxybutynin [24, 25] in respective trials.

3.1.2. Tolterodine. Tolderodine is a widely prescribed antimuscarinic and, it was the first specifically developed to treat OAB. Tolterodine is not selective for any muscarinic receptor subtype, but it exhibits selectivity for the urinary bladder over salivary glands in vivo [26].

An IR formulation was available first, but an ER, administered once daily, formulation was later designed. Its efficacy and tolerability have been proved in a large number of trials [27]. Tolterodine offers significant improvement in overactive bladder symptoms and quality of life while having a favorable safety profile. It soon became the gold standard in the class, a drug that all others are compared to, during their clinical development.

Oxybutynin and tolterodine, the until relatively recent years most commonly prescribed antimuscarinics, have been shown to have similar efficacies in general OAB populations [28], as well as in specific subpopulations defined by severity of urodynamic findings [29].

3.1.3. Propiverine. Propiverine, another muscarinic receptor antagonist, has also been demonstrated to inhibit L-type Ca^{++} channels in high concentrations [30].

Propiverine has similar efficacy to oxybutynin and tolterodine, similar tolerability and impact on quality of life to tolterodine, but a better tolerability profile than oxybutynin [31, 32]. This drug is well tolerated [33].

Propiverine and oxybutynin are efficacious in children with incontinence due to overactive bladder and propiverine is officially approved in certain countries for pediatric use. Alloussi et al. [34] evaluated existing evidence for the use of antimuscarinics in children. They concluded that high-quality studies are still limited and results vary widely across antimuscarinics. This fact is associated with different levels of evidence and grades of recommendation for children for oxybutynin (3 C), propiverine (1 B/C), tolterodine (3 C), and trospium chloride (3 C), awarded by the International Consultation on Incontinence. The daily urgency episodes were significantly reduced from baseline to 12 weeks on propiverine treatment, compared with placebo. Secondary endpoints, including sum of urgency severity per 24 h, urgency severity per void, and daytime voiding frequency, were also improved significantly in the propiverine group [35].

3.1.4. Darifenacin. Darifenacin is the antimuscarinic with the highest M-3 receptor subtype selectivity. Long-term darifenacin treatment was associated with significant and clinically meaningful improvements in quality of life of patients with urge incontinence ("wet" OAB) over 2 years [36]. In a study of patients who were dissatisfied with their previous treatment with oxybutynin ER or tolderodine ER, patients perception of bladder condition (PPBC) score and OAB symptoms were significantly improved, and satisfaction was high during treatment with darifenacin 7.5 or 15 mg [37]. Haab [14] in a comprehensive review described the good clinical efficacy and safety profile of this agent.

3.1.5. Solifenacin. A pooled analysis of four randomized, placebo-control1ed, phase III studies of solifenacin in OAB patients without incontinence, showed a significant improvement of symptoms and voided volume after 12 weeks of treatment [38].

How does solifenacin compare to longer established antimuscarinics? One comparison of the "new" (solifenacin and darifenacin) and "old" antimuscarinic agents showed the two generations of treatment had similar efficacy [35, 39]. A randomized, double-blind study found that solifenacin is superior to an encapsulated formulation of tolterodine ER in most of the efficacy outcomes [40]. The majority of side effects were mild to moderate in nature, yet significantly

more for solifenacin, and discontinuations were comparable and low in both groups. This study investigated both approved doses of solifenacin, 5 mg and 10 mg, and was, therefore, criticized for using doses not directly comparable to tolterodine 4 mg. A subanalysis of this study [30] subsequent compared solifenacin 5 mg and tolderodine 4 mg and better reflected treatment outcomes with the doses most commonly used in clinical practice, at least during treatment initiation. It concluded that after a 4-weeks treatment period, solifenacin 5 mg significantly improved incontinence symptoms and reduced the use of incontinent pads, compared to tolterodine. In another, randomized, placebo-controlled study, Cardozo et al. [41] found that solifenacin significantly reduced the number of urgency episodes and urgency bother and was well tolerated. Treatment was effective as early as day 3.

Solifenacin is the first antimuscarinic to demonstrate significant warning-time improvement in a large OAB clinical trial conducted to evaluate warning time and diary variables in the same study population [42].

A relatively recent comprehensive review for solifenacin concluded that this agent was effective in the treatment of OAB with urge incontinence [12].

3.1.6. Trospium. Trospium chloride is a quaternary ammonium compound. It does not cross the blood-brain barrier; therefore, no central nervous system adverse events are anticipated [16]. This drug significantly reduces UUI and frequency compared with placebo [43]. Compared to tolderodine, trospium reduced the frequency of micturition and incontinence episodes. Extended-release trospium chloride 60 mg, a novel modified-release form of this compound allows once-daily administration, potentially enhancing compliance to treatment and improving its clinical efficacy/tolerability profile, compared with immediate-release form [44]. Cardozo et al. [44] in a recent publication underlined that the extent of metabolism of this drug is low and independent of the liver cytochrome P450 isoenzyme system. This pharmacodynamic profile further simplifies decision making in polypharmacy situations, such as multimorbid and elderly patients. Furthermore, subject to predominantly renal elimination as the unchanged form, trospium chloride retains its pharmacological activity within the urinary bladder, and local action on urothelium muscarinic receptors is supposed to contribute to its early onset and sustained efficacy in controlling urgency.

3.1.7. Fesoterodine. Fesoterodine is the newest antimuscarinic for the treatment of OAB. Fesoterodine is a prodrug. It is rapidly and extensively hydrolyzed by nonspecific esterases, thus bypassing the CYP system, to 5-hydroxymethyl tolderodine (5-HMT), which is also the active metabolite of tolderodine. Interestingly, as 5-HMT formation from fesoterodine occurs via ubiquitous nonspecific esterases, the rate of fesoterodine hydrolyzation maybe more uniform and complete.

Initial data from phase 2 trials showed that fesoterodine was an effective and well-tolerated therapy for OAB [45]. In subsequent clinical studies, fesoterodine doses of 4 and 8 mg/day were consistently superior to placebo in improving overactive bladder symptoms, with 8 mg/day having significantly greater effects than 4 mg/day [17]. Both doses were safe and well tolerated, with a low overall incidence of adverse events. Tolerability is comparable to that of tolderodine (ER) [46].

In a posthoc analysis of pooled data from two clinical trials including 1,548 women with overactive bladder, fesoterodine 4 mg and 8 mg and tolderodine showed significant improvements in all bladder diary variables assessed and greater response rates versus placebo. Fesoterodine 8 mg was significantly more efficacious than fesoterodine 4 mg and tolderodine ER in improving UUI episodes and continence days per week [47]. Recently, the FACT study, a head to head placebo controlled trial, compared the efficacy and tolerability of fesoterodine 8 mg with tolderodine ER 4 mg. This study was designed to asses the superiority of fesoterodine over tolderodine ER for the treatment of OAB symptoms, and 1697 patients were included. This trial concluded that in patients with OAB, fesoterodine 8 mg showed superior efficacy over tolderodine ER 4 mg and placebo in reducing UUI episodes and in improving most patient-reported outcome measures. Both active treatments were well tolerated [48]. In another recent study, the flexible dose of fesoterodine was evaluated. Among 516 subjects treated, approximately 50% opted for dose escalation to 8 mg at week 4. The study concluded that flexible dose fesoterodine significantly improved OAB symptoms health related quality of life (HRQOL) and rates of treatment satisfaction and was well tolerated in patients with OAB who were dissatisfied with prior tolderodine therapy [49].

3.2. Efficacy and Safety. Currently available antimuscarinics have all demonstrated their efficacy and safety in well-designed, controlled studies conducted during their clinical development. The significant placebo effect observed in OAB trials and the frequent treatment discontinuations in real-life practice have often raised doubts regarding the true efficacy and/or safety of this drug class. Systematic reviews and meta-analyses of existing data have tried to clarify uncertainties.

In 2003, Herbison et al. [39] have published a systematic review of randomized controlled trials comparing antimuscarinic agents to placebo in the treatment of OAB. The authors concluded that antimuscarinic drug therapy provided significant improvement in OAB symptoms, such as urge incontinence episodes and micturition frequency over placebo. Significant improvements, compared to placebo have also been demonstrated for urodynamic parameters. However, the magnitude of treatment effect was smaller than the anticipated based on clinical experience with antimuscarinics. A possible explanation for this is the common combination of medical treatment and bladder training in clinical practice. In the majority of clinical trials, formal bladder training is not included.

A 2005 systematic review of 52 randomized, controlled trials by Chapple et al. [50], which was latter updated with more studies in 2008 [51], showed that antimuscarinics, as a class, significantly reduce urge incontinence episodes, making many patients continent, and provide significant

improvements in quality of life. They also reduce the severity of urgency and decrease micturition frequency. Individual antimuscarinics were effective in at least one of the outcome measures included in the reviews. Profiles of each drug and dosage differ and should be considered in making treatment choices. Despite abundance of evidence on the short-term efficacy of antimuscarinics, Chapple et al. noted a lack of knowledge regarding issues of chronic treatment, given that followup in most trials is short.

Differences in efficacy of antimuscarinics have often reached statistical significance in clinical trials. Nevertheless, the magnitude of these differences is not readily appreciated in everyday clinical practice and many clinicians consider drugs in this class as "comparable" in terms of efficacy. According to a meta-analysis by Novara et al. [24], efficacies of available antimuscarinics are comparable. Nevertheless, if factors such as safety, tolerability, and cost are to be taken into account, Oxybutynin ER, tolterodine ER 4 mg, solifenacin 5 mg, or solifenacin 10 mg can be considered the first-line treatment choice. Darifenacin 15 mg and fesoterodine 4 mg are alternatives although more data are needed. In cases of lack of efficacy of first-line ER drug, fesoterodine 8 mg and solifenacin 10 mg might be second-line treatment, given that their efficacy is superior with only a small compromise in tolerability.

As far as safety is concerned, antimuscarinics, in general, are safe [24, 52, 53]. The "older" drugs oxybutynin and tolterodine have been more thoroughly studied [54, 55]. Side effects are due to muscarinic receptor binding in organs other than the bladder. The effects of antimuscarinics on salivary glands are responsible for the most common and bothersome side effect, dry mouth. Other unwanted effects include constipation, blurred vision, somnolence, dizziness and cognitive impairment. Untreated, close-angle glaucoma is a contraindication for antimuscarinics.

Slight differences in the safety profiles of existing antimuscarinic agents depend on their selectivity for specific muscarinic receptor subtypes, selectivity for the bladder compared to salivary glands, their lipophilicity and ability to cross the blood-brain barrier, as well as their pharmacokinetic properties.

Evidence from controlled trials [50] suggests that antimuscarinics are well tolerated compared with placebo, with the exception of immediate-release (IR) oxybutynin. Extended-release (ER) tolterodine is the only formulation with fewer total treatment discontinuations compared with placebo, a finding that just reached statistical significance.

In general, the extended release formulations are better tolerated than the immediate release ones. In cases that dry mouth is intolerable with the oral formulations, transdermal oxybutynin might bean alternative, but, unfortunately, application site reactions are common with the oxybutynin patch [21]. Solifenacin and darifenacin are believed to be associated with higher rates of constipation [24] compared to other antimuscarinics. Nevertheless, a recent meta-analysis of randomized, placebo-controlled trials has shown high odds ratios for constipation, compared with placebo, for other drugs as well [56].

Central nervous system side effects are a concern when prescribing antimuscarinics for the treatment of OAB, particularly in vulnerable populations such as the elderly and CNS-compromised, neurogenic bladder patients. The evidence for cognitive impairment with oxybutynin is compelling [57]. Darifenacin with low CNS penetration and selectivity for the M3 over the M1 muscarinic receptor subtype is expected to cause less cognitive impairment. Indeed, in a short term study, darifenacin did not have any effect on the cognitive function [58]. Moreover, a review of available literature [59] concluded that darifenacin did not cause an impairment of memory among other cognitive functions. Trospium chloride is another drug that does not cross the blood-brain barrier and in a recent study it was undetectable in the older human central nervous system [60]. Fesoterodine is considerably less lipophilic than tolderodine [61] which has minimal or no cognitive effects.

The binding of muscarinic receptors in the heart may lead to cardiovascular adverse events and QT interval prolongation has been a concern with antimuscarinics. In a randomized, double-blind, placebo-controlled, crossover trial [62], tolterodine significantly increased heart rate versus placebo and darifenacin did not affect heart rate compared to placebo. Darifenacin does not prolong QT/QTc interval [63]. An older study showed that Oxybutynin is not associated with a corrected QT interval prolongation and is unlikely to induce ventricular arrhythmias [64]. It seems that tolterodine does not have a clinically significant effect on QT interval [65]. Propiverine provoked a statistically significant increase in the mean QTc interval but without clinical arrhythmic events [66]. The newest antimuscarinic drug fesoterodine is not associated with QTc prolongation or other ECG abnormalities at either therapeutic or supratherapeutic doses [67]. In a study with real-life conditions, that is, with inclusion of large numbers of patients with cardiovascular comorbidities and taking several other medications, therapeutically effective doses of solifenacin did not increase heart rate or blood pressure [68].

3.3. Special Treatment Issues

3.3.1. Treatment Compliance. Despite acceptable rates of treatment discontinuation in clinical trials, real-life compliance, especially to long-term treatment, is low. For example, in a pharmacy dispensing records review for antimuscarinic agents from January 2003 to December 2006 conducted for the United States Military Health System National Capital Region, 35% of OAB patients did not refill a fully reimbursed prescription for antimuscarinics [69]. In another study, 44.5% of patients did not renew their first prescription of antimuscarinics [70]. In observational trials, under real-life conditions, discontinuation rates for tolterodine, for example, have been reported to be as high as 49% at 6 months followup [71]. Overall, adherence is significantly better for extended release than immediate release agents.

Low compliance to treatment can be due to inadequate drug efficacy, intolerable side effects, poor patient education and follow up, and cost issues. Among these reasons dry mouth is the most common [51, 72]. In every-day

clinical practice, unmet expectations may represent another important reason for treatment discontinuation [73, 74]. Selecting the appropriate drug for each patient, the one that offers the best balance between efficacy and adverse events would be a very important step in improving adherence to treatment. Patient education on OAB and its treatments and patient reassurance when side effects occur represent other important strategies in improving compliance. Realistic patient expectations from treatment are a prerequisite for treatment success.

3.3.2. Dose Flexibility. Dose flexibility offers the advantage of an individually tailored treatment to achieve the optimum balance between efficacy and adverse events. A strategy based on patient-requested dose increases has been found to consistently improve overactive bladder symptoms. The impact of dose flexibility on clinical management of OAB has been examined in studies with solifenacin, darifenacin, and oxybutynin ER [75]. Patients requesting a dose increase usually had more severe symptoms at baseline than those who did not request uptitration. Patients with severe symptoms at baseline benefit more from the increased dose [75]. In clinical trials, about 50% of the patients ask for an increase of the dose of their medication [40, 49]. Selecting a drug which offers dose flexibility seams a reasonable first-line treatment approach.

3.3.3. Switch between Antimuscarinics. Despite the fact that differences in efficacy of antimuscarinics in clinical trials with large OAB populations are relatively small, an individual patient may benefit more from a particular drug than another. "Salvaging" nonresponders to one drug with another has been shown in several studies. Solifenacin, for example, has been shown to significantly improve bladder diary and validated quality-of-life outcomes in women with urge incontinence that failed to respond or were unable to tolerate oxybutynin IR [75]. Solifenacin treatment in patients with residual urgency after an at-least-four-week course of tolterodine ER 4 mg was associated with significant improvements in urgency and other diary-documented symptoms of OAB. Patients treated with solifenacin also had significant improvements in quality of life scores and the perceived bother of OAB [76]. In another study, patient's perception of bladder condition (PPBC) score and OAB symptoms were significantly improved, and satisfaction was high during treatment with darifenacin (7.5/15 mg) in patients who were dissatisfied with the previous oxybutynin ER or tolterodine ER treatment [37]. In a recent study [77], patients dissatisfied with tolterodine received fesoterodine 4 mg or 8 mg. PPBC, urgency perception scale and the overactive bladder questionnaire (OAB-q) were significantly improved after 12 weeks of fesoterodine and 80% of patients became satisfied.

The above studies, despite limitations in patient selection and overall design, suggest that switch between drugs is a reasonable approach in patient failing initial treatment.

3.3.4. Safety in the Male Population. A significant concern when antimuscarinics are considered in male patients with storage lower urinary tract symptoms (LUTS), suggestive of an overactive bladder, is the risk of urinary retention. This concern seems particularly relevant when voiding, benign prostate hyperplasia-related LUTS are present. The reality, nevertheless, is that antimuscarinics at clinically recommended doses have little effect on voiding pressures. Clinical experience has proved that concerns regarding acute urinary retention or increased residual volume are unfounded [78–83]. The incidence of urinary retention is minimal (<1%), even in male patients with bladder outflow obstruction, despite the occasional increase in residual urine in certain patients. On the other hand, there are no established criteria for excluding patients at risk for retention from antimuscarinic therapy [81]. More studies with large number of patients, including patients with severe obstruction, are required. In the meantime, it seems reasonable to offer antimuscarinics, either as monotherapy or in combination with α-blockers to men with mild-to-moderate obstruction and small residual volumes. The addition of an antimuscarinic to a-blockers has been shown to significantly improve symptoms and quality of life of these patients [79, 81, 84, 85].

4. Conclusions

Antimuscarinic agents, as a class, are the cornerstone of medical treatment of overactive bladder. Accumulated evidence from clinical trials and meta-analyses has proved their efficacy and safety. Antimuscarinics offer significant improvements in symptoms of urge incontinence, urgency, frequency, and nocturia. This translates in substantial benefits in quality of life. Antimuscarinics are generally well tolerated with mild and predictable antimuscarinic side effects. The most common and bothersome of them, dry-mouth, not infrequently leads to treatment discontinuation.

Available antimuscarinics have small, yet statistically significant, differences in their efficacy and tolerability profiles. In general, the higher doses of drugs that offer dose flexibility have higher efficacy. Tolerability depends mainly on drug selectivity for the bladder over other organs, selectivity for muscarinic receptor subtypes and ability to penetrate the CNS. Given that there is no "cure" for OAB yet, finding the agent that offers the optimum balance of efficacy and side effects for an individual patient remains the major challenge in OAB treatment.

Disclosure

A. Athanasopoulos is or has been an investigator, lecturer and consultant for pharmaceutical companies producing or developing drugs for lower urinary tract symptoms (Pfizer, Astellas, Ucb, Lilly, Allergan, Bard, and Amgen). K. Giannitsas is or has been an investigator and lecturer for pharmaceutical companies producing or developing drugs for lower urinary tract symptoms (Pfizer, Astellas, Lilly, and Allergan).

References

[1] H. Hashim and P. Abrams, "Overactive bladder: an update," *Current Opinion in Urology*, vol. 17, no. 4, pp. 231–236, 2007.

[2] K.-E. Andersson, "Antimuscarinic mechanisms and the overactive detrusor: an update," *European Urology*, vol. 59, no. 3, pp. 377–386, 2011.

[3] O. Yamaguchi, "Antimuscarinics and overactive bladder: other mechanism of action," *Neurourology and Urodynamics*, vol. 29, no. 1, pp. 112–115, 2010.

[4] D. Giglio and G. Tobin, "Muscarinic receptor subtypes in the lower urinary tract," *Pharmacology*, vol. 83, no. 5, pp. 259–269, 2009.

[5] K. E. Andersson and C. R. Chappie, "Oxybutynin and the overactive bladder," *World Journal of Urology*, vol. 19, no. 5, pp. 319–323, 2001.

[6] S. De Wachter and J. J. Wyndaele, "Intravesical oxybutynin: a local anesthetic effect on bladder C afferents," *Journal of Urology*, vol. 169, no. 5, pp. 1892–1895, 2003.

[7] G. W. Davila, "Transdermal oxybutynin: a new treatment for overactive bladder," *Expert Opinion on Pharmacotherapy*, vol. 4, no. 12, pp. 2315–2324, 2003.

[8] M. A. A. Siddiqui, C. M. Perry, and L. J. Scott, "Oxybutynin extended-release: a review of its use in the management of overactive bladder," *Drugs*, vol. 64, no. 8, pp. 885–912, 2004.

[9] J. Wefer, M. C. Truss, and U. Jonas, "Tolterodine: an overview," *World Journal of Urology*, vol. 19, no. 5, pp. 312–318, 2001.

[10] H. Madersbacher and G. Mürtz, "Efficacy, tolerability and safety profile of propiverine in the treatment of the overactive bladder (non-neurogenic and neurogenic)," *World Journal of Urology*, vol. 19, no. 5, pp. 324–335, 2001.

[11] D. Robinson and L. Cardozo, "The emerging role of solifenacin in the treatment of overactive bladder," *Expert Opinion on Investigational Drugs*, vol. 13, no. 10, pp. 1339–1348, 2004.

[12] M. Maniscalco, D. Singh-Franco, W. R. Wolowich, and R. Torres-Colón, "Solifenacin succinate for the treatment of symptoms of overactive bladder," *Clinical Therapeutics*, vol. 28, no. 9, pp. 1247–1272, 2006.

[13] C. R. Chapple, "Darifenacin: a novel M3 muscarinic selective receptor antagonist for the treatment of overactive bladder," *Expert Opinion on Investigational Drugs*, vol. 13, no. 11, pp. 1493–1500, 2004.

[14] F. Haab, "Darifenacin for the treatment of overactive bladder," *Women's Health*, vol. 1, pp. 331–343, 2005.

[15] K. Hofner, M. Oelke, S. Machtens, and V. Grünewald, "Trospium chloride—an effective drug in the treatment of overactive bladder and detrusor hyperreflexia," *World Journal of Urology*, vol. 19, no. 5, pp. 336–343, 2001.

[16] E. S. Rovner, "Trospium chloride in the management of overactive bladder," *Drugs*, vol. 64, no. 21, pp. 2433–2446, 2004.

[17] M. C. Michel, "Fesoterodine: a novel muscarinic receptor antagonist for the treatment of overactive bladder syndrome," *Expert Opinion on Pharmacotherapy*, vol. 9, no. 10, pp. 1787–1796, 2008.

[18] T. Hanawa, C. Tsuchiya, N. Endo et al., "Formulation study of intravesical oxybutynin instillation solution with enhanced retention in bladder," *Chemical and Pharmaceutical Bulletin*, vol. 56, no. 8, pp. 1073–1076, 2008.

[19] A. C. Diokno, R. A. Appell, P. K. Sand et al., "Prospective, randomized, double-blind study of the efficacy and tolerability of the extended-release formulations of oxybutynin and tolterodine for overactive bladder: results of the OPERA trial," *Mayo Clinic Proceedings*, vol. 78, no. 6, pp. 687–695, 2003.

[20] R. A. Appell, P. Sand, R. Dmochowski, R. Anderson, and N. Zinner, "Prospective randomized controlled trial of extended-release oxybutynin chloride and tolterodine tartrate in the treatment of overactive bladder: results of the OBJECT study," *Mayo Clinic Proceedings*, vol. 76, no. 4, pp. 358–363, 2001.

[21] P. Sand, N. Zinner, D. Newman et al., "Oxybutynin transdermal system improves the quality of life in adults with overactive bladder: a multicentre, community-based, randomized study," *British Journal of Urology International*, vol. 99, no. 4, pp. 836–844, 2007.

[22] L. T. Pizzi, A. Talati, E. Gemmen, N. V. Dahl, T. J. Bunz, and P. K. Sand, "Impact of transdermal oxybutynin on work productivity in patients with overactive bladder: results from the MATRIX study," *PharmacoEconomics*, vol. 27, no. 4, pp. 329–339, 2009.

[23] D. R. Staskin and D. Robinson, "Oxybutynin chloride topical gel: a new formulation of an established antimuscarinic therapy for overactive bladder," *Expert Opinion on Pharmacotherapy*, vol. 10, no. 18, pp. 3103–3111, 2009.

[24] G. Novara, A. Galfano, S. Secco et al., "A systematic review and meta-analysis of randomized controlled trials with antimuscarinic drugs for overactive bladder," *European Urology*, vol. 54, no. 4, pp. 740–764, 2008.

[25] J. F. Guest, D. Abegunde, and F. J. Ruiz, "Cost effectiveness of controlled-release oxybutynin compared with immediate-release oxybutynin and tolterodine in the treatment of overactive bladder in the UK, France and Austria," *Clinical Drug Investigation*, vol. 24, no. 6, pp. 305–321, 2004.

[26] L. Nilvebrant, B. Hallén, and G. Larsson, "Tolterodine A new bladder selective muscarinic receptor antagonist: preclinical pharmacological and clinical data," *Life Sciences*, vol. 60, no. 13-14, pp. 1129–1136, 1997.

[27] S. Salvatore, M. Serati, and P. Bolis, "Tolterodine for the treatment of overactive bladder," *Expert Opinion on Pharmacotherapy*, vol. 9, no. 7, pp. 1249–1255, 2008.

[28] P. Abrams, R. Freeman, C. Anderström, and A. Mattiasson, "Tolterodine, a new antimuscarinic agent: as effective but better tolerated than oxybutynin in patients with an overactive bladder," *British Journal of Urology*, vol. 81, no. 6, pp. 801–810, 1998.

[29] K. Giannitsas, P. Perimenis, A. Athanasopoulos, K. Gyftopoulos, G. Nikiforidis, and G. Barbalias, "Comparison of the efficacy of tolterodine and oxybutynin in different urodynamic severity grades of idiopathic detrusor overactivity," *European Urology*, vol. 46, no. 6, pp. 776–782, 2004.

[30] H. Madersbacher and G. Mürtz, "Efficacy, tolerability and safety profile of propiverine in the treatment of the overactive bladder (non-neurogenic and neurogenic)," *World Journal of Urology*, vol. 19, no. 5, pp. 324–335, 2001.

[31] H. Madersbacher, M. Halaska, R. Voigt, S. Alloussi, and K. Höfner, "A placebo-controlled, multicentre study comparing the tolerability and efficacy of propiverine and oxybutynin in patients with urgency and urge incontinence," *British Journal of Urology International*, vol. 84, no. 6, pp. 646–651, 1999.

[32] K. P. Jünemann, M. Halaska, T. Rittstein et al., "Propiverine versus tolterodine: efficacy and tolerability in patients with overactive bladder," *European Urology*, vol. 48, no. 3, pp. 478–482, 2005.

[33] H. Madersbacher and G. Mürtz, "Efficacy, tolerability and safety profile of propiverine in the treatment of the overactive bladder (non-neurogenic and neurogenic)," *World Journal of Urology*, vol. 19, no. 5, pp. 324–335, 2001.

[34] S. H. Alloussi, G. Murtz, J. Seibold et al., "Antimuscarincs in children: is its use in children evidence-based?" *International Urogynecology Journal*, vol. 21, supplement 1, p. 428, 2010, abstract 292.

[35] K. S. Lee, H. W. Lee, M. S. Choo et al., "Urinary urgency outcomes after propiverine treatment for an overactive bladder: the 'Propiverine study on overactive bladder including urgency data," *British Journal of Urology International*, vol. 105, no. 11, pp. 1565–1570, 2010.

[36] P. Dwyer, C. Kelleher, J. Young et al., "Long-term benefits of darifenacin treatment for patient quality of life: results from a 2-year extension study," *Neurourology and Urodynamics*, vol. 27, no. 6, pp. 540–547, 2008.

[37] N. Zinner, K. C. Kobashi, U. Ebinger et al., "Darifenacin treatment for overactive bladder in patients who expressed dissatisfaction with prior extended-release antimuscarinic therapy," *International Journal of Clinical Practice*, vol. 62, no. 11, pp. 1664–1674, 2008.

[38] P. Abrams and S. Swift, "Solifenacin is effective for the treatment of OAB dry patients: a pooled analysis," *European Urology*, vol. 48, no. 3, pp. 483–487, 2005.

[39] P. Herbison, J. Hay-Smith, G. Ellis, and K. Moore, "Effectiveness of anticholinergic drugs compared with placebo in the treatment of overactive bladder: systematic review," *British Medical Journal*, vol. 326, no. 7394, pp. 841–844, 2003.

[40] C. R. Chapple, R. Martinez-Garcia, L. Selvaggi et al., "A comparison of the efficacy and tolerability of solifenacin succinate and extended release tolterodine at treating overactive bladder syndrome: results of the STAR trial," *European Urology*, vol. 48, no. 3, pp. 464–470, 2005.

[41] L. Cardozo, E. Heßdörfer, R. Milani et al., "Solifenacin in the treatment of urgency and other symptoms of overactive bladder: results from a randomized, double-blind, placebo-controlled, rising-dose trial," *British Journal of Urology International*, vol. 102, no. 9, pp. 1120–1127, 2008.

[42] M. M. Karram, M. R. Toglia, S. R. Serels, M. Andoh, A. Fakhoury, and S. Forero-Schwanhaeuser, "Treatment with solifenacin increases warning time and improves symptoms of overactive bladder: results from VENUS, a randomized, double-blind, placebo-controlled trial," *Urology*, vol. 73, no. 1, pp. 14–18, 2009.

[43] N. Zinner, M. Gittelman, R. Harris, J. Susset, A. Kanellos, and S. Auerbach, "Trospium chloride improves overactive bladder symptoms: a multicenter phase III trial," *Journal of Urology*, vol. 171, no. 6 I, pp. 2311–2315, 2004.

[44] L. Cardozo, V. Mirone, C. Gratzke, and M. Marberger, "Extended-release trospium chloride 60 mg—a new once-daily medication for the treatment of overactive bladder syndrome," *European Urological Review*, vol. 5, no. 1, pp. 3–6, 2010.

[45] V. Nitti, M. Wiatrak, L. Kreitman, and D. Lipsitz, Fesoterodine is an effective antimuscarinic for patients with overactive bladder (OAB)Q results of a phase 2 trial. Paper presented at International Continence Society Montreal, Canada, 2005.

[46] C. Chapple, P. Van Kerrebroeck, A. Tubaro et al., "Clinical efficacy, safety, and tolerability of once-daily fesoterodine in subjects with overactive bladder," *European Urology*, vol. 52, no. 4, pp. 1204–1212, 2007.

[47] S. A. Kaplan, T. Schneider, J. E. Foote, Z. Guan, M. Carlsson, and J. Gong, "Superior efficacy of fesoterodine over tolterodine extended release with rapid onset: a prospective, head-to-head, placebo-controlled trial," *British Journal of Urology International*, vol. 107, no. 9, pp. 1432–1440, 2011.

[48] S. Herschorn, S. Swift, Z. Guan et al., "Comparison of fesoterodine and tolterodine extended release for the treatment of overactive bladder: a head-to-head placebo-controlled trial," *British Journal of Urology International*, vol. 105, no. 1, pp. 58–66, 2010.

[49] J.-J. Wyndaele, E. R. Goldfischer, J. D. Morrow et al., "Effects of flexible-dose fesoterodine on overactive bladder symptoms and treatment satisfaction: an open-label study," *International Journal of Clinical Practice*, vol. 63, no. 4, pp. 560–567, 2009.

[50] C. Chapple, V. Khullar, Z. Gabriel, and J. A. Dooley, "The effects of antimuscarinic treatments in overactive bladder: a systematic review and meta-analysis," *European Urology*, vol. 48, no. 1, pp. 5–26, 2005.

[51] C. R. Chapple, V. Khullar, Z. Gabriel, D. Muston, C. E. Bitoun, and D. Weinstein, "The effects of antimuscarinic treatments in overactive bladder: an update of a systematic review and meta-analysis," *European Urology*, vol. 54, no. 3, pp. 543–562, 2008.

[52] C. R. Chapple, V. Khullar, Z. Gabriel, D. Muston, C. E. Bitoun, and D. Weinstein, "The effects of antimuscarinic treatments in overactive bladder: an update of a systematic review and meta-analysis," *European Urology*, vol. 54, no. 3, pp. 543–562, 2008.

[53] L. P. W. Witte, W. M. C. Mulder, J. J. M. C. H. De La Rosette, and M. C. Michel, "Muscarinic receptor antagonists for overactive bladder treatment: does one fit all?" *Current Opinion in Urology*, vol. 19, no. 1, pp. 13–19, 2009.

[54] R. Millard, J. Tuttle, K. Moore et al., "Clinical efficacy and safety of tolterodine compared to placebo in detrusor overactivity," *Journal of Urology*, vol. 161, no. 5, pp. 1551–1555, 1999.

[55] Y. E. Yarker, K. L. Goa, and A. Fitton, "Oxybutynin. A review of its pharmacodynamic and pharmacokinetic properties, and its therapeutic use in detrusor instability," *Drugs & Aging*, vol. 6, no. 3, pp. 243–262, 1995.

[56] P. D. Meek, S. D. Evang, M. Tadrous, D. Roux-Lirange, D. M. Triller, and B. Gumustop, "Overactive bladder drugs and constipation: a meta-analysis of randomized, placebo-controlled trials," *Digestive Diseases and Sciences*, vol. 56, no. 1, pp. 7–18, 2011.

[57] G. Kay, T. Crook, L. Rekeda et al., "Differential effects of the antimuscarinic agents darifenacin and oxybutynin ER on memory in older subjects," *European Urology*, vol. 50, no. 2, pp. 317–326, 2006.

[58] R. B. Lipton, K. Kolodner, and K. Wesnes, "Assessment of cognitive function of the elderly population: effects of darifenacin," *Journal of Urology*, vol. 173, no. 2, pp. 493–498, 2005.

[59] G. G. Kay and U. Ebinger, "Preserving cognitive function for patients with overactive bladder: evidence for a differential effect with darifenacin," *International Journal of Clinical Practice*, vol. 62, no. 11, pp. 1792–1800, 2008.

[60] D. Staskin, G. Kay, C. Tannenbaum et al., "Trospium chloride is undetectable in the older human central nervous system," *Journal of the American Geriatrics Society*, vol. 58, no. 8, pp. 1618–1619, 2010.

[61] B. Malhotra, K. Gandelman, R. Sachse, N. Wood, and M. C. Michel, "The design and development of fesoterodine as a prodrug of 5-hydroxymethyl tolterodine (5-HMT), the active metabolite of tolterodine," *Current Medicinal Chemistry*, vol. 16, no. 33, pp. 4481–4489, 2009.

[62] B. Olshansky, U. Ebinger, J. Brum, M. Egermark, A. Viegas, and L. Rekeda, "Differential pharmacological effects of antimuscarinic drugs on heart rate: a randomized, placebo-controlled, double-blind, crossover study with tolterodine and

darifenacin in healthy participants ≥50 years," *Journal of Cardiovascular Pharmacology and Therapeutics*, vol. 13, no. 4, pp. 241–251, 2008.

[63] D. B. Serra, M. B. Affrime, M. P. Bedigian et al., "QT and QTc interval with standard and supratherapeutic doses of darifenacin, a muscarinic M selective receptor antagonist for the treatment of overactive bladder," *Journal of Clinical Pharmacology*, vol. 45, no. 9, pp. 1038–1047, 2005.

[64] R. M. Hussain, K. Hartigan-Go, S. H. L. Thomas, and G. A. Ford, "Effect of oxybutynin on the QTc interval in elderly patients with urinary incontinence," *British Journal of Clinical Pharmacology*, vol. 41, no. 1, pp. 73–75, 1996.

[65] B. K. Malhotra, P. Glue, K. Sweeney, R. Anziano, J. Mancuso, and P. Wicker, "Thorough QT study with recommended and supratherapeutic doses of tolterodine," *Clinical Pharmacology and Therapeutics*, vol. 81, no. 3, pp. 377–385, 2007.

[66] Y. Homma and O. Yamaguchi, "A randomized, double-blind, placebo- and propiverine-controlled trial of the novel antimuscarinic agent imidafenacin in Japanese patients with overactive bladder," *International Journal of Urology*, vol. 16, no. 5, pp. 499–506, 2009.

[67] B. Malhotra, N. Wood, R. Sachse, and K. Gandelman, "Thorough QT study of the effect of fesoterodine on cardiac repolarization," *International Journal of Clinical Pharmacology and Therapeutics*, vol. 48, no. 5, pp. 309–318, 2010.

[68] M. C. Michel, U. Wetterauer, M. Vogel, and J. J. De La Rosette, "Cardiovascular safety and overall tolerability of solifenacin in routine clinical use: a 12-week, open-label, post-marketing surveillance study," *Drug Safety*, vol. 31, no. 6, pp. 505–514, 2008.

[69] C. L. G. Sears, C. Lewis, K. Noel, T. S. Albright, and J. R. Fischer, "Overactive bladder medication adherence when medication is free to patients," *Journal of Urology*, vol. 183, no. 3, pp. 1077–1081, 2010.

[70] A. O. D'Souza, M. J. Smith, L. A. Miller, J. Doyle, and R. Ariely, "Persistence, adherence, and switch rates among extended-release and immediate-release overactive bladder medications in a regional managed care plan," *Journal of Managed Care Pharmacy*, vol. 14, no. 3, pp. 291–301, 2008.

[71] R. Peeker, G. Samsioe, J. Kowalski, A.-S. Andersson, and A. Bergqvist, "A prospective observational study of the effects of treatment with extended-release tolterodine on health-related quality of life of patients suffering overactive bladder syndrome in Sweden," *Scandinavian Journal of Urology and Nephrology*, vol. 44, no. 3, pp. 138–146, 2010.

[72] C. R. Chapple, A. Fianu-Jonsson, M. Indig et al., "Treatment outcomes in the STAR study: a subanalysis of solifenacin 5 mg and tolterodine ER 4 mg," *European Urology*, vol. 52, no. 4, pp. 1195–1203, 2007.

[73] F. Haab and D. Castro-Diaz, "Persistence with antimuscarinic therapy in patients with overactive bladder," *International Journal of Clinical Practice*, vol. 59, no. 8, pp. 931–937, 2005.

[74] J. S. Benner, M. B. Nichol, E. S. Rovner et al., "Patient-reported reasons for discontinuing overactive bladder medication," *British Journal of Urology International*, vol. 105, no. 9, pp. 1276–1282, 2010.

[75] C. R. Chapple, M. T. Rosenberg, and F. J. Brenes, "Listening to the patient: a flexible approach to the use of antimuscarinic agents in overactive bladder syndrome," *British Journal of Urology International*, vol. 104, no. 7, pp. 960–967, 2009.

[76] M. B. Chancellor, N. Zinner, K. Whitmore et al., "Efficacy of solifenacin in patients previously treated with tolterodine extended release 4 mg: results of a 12-week, multicenter, open-label, flexible-dose study," *Clinical Therapeutics*, vol. 30, no. 10, pp. 1766–1781, 2008.

[77] J.-J. Wyndaele, E. R. Goldfischer, J. D. Morrow, J. Gong, L.-J. Tseng, and M.-S. Choo, "Patient-optimized doses of fesoterodine improve bladder symptoms in an open-label, flexible-dose study," *British Journal of Urology International*, vol. 107, no. 4, pp. 603–611, 2011.

[78] A. Athanasopoulos and P. Perimenis, "Efficacy of the combination of an α1-blocker with an anticholinergic agent in the treatment of lower urinary tract symptoms associated with bladder outlet obstruction," *Expert Opinion on Pharmacotherapy*, vol. 6, no. 14, pp. 2429–2433, 2005.

[79] A. Athanasopoulos, "Antimuscarinics and bladder outlet obstruction: from a contraindication to an indication?" *Neurourology and Urodynamics*, vol. 29, supplement 1, pp. S46–S50, 2010.

[80] A. Athanasopoulos, D. Mitropoulos, K. Giannitsas, and P. Perimenis, "Safety of anticholinergics in patients with benign prostatic hyperplasia," *Expert Opinion on Drug Safety*, vol. 7, no. 4, pp. 473–479, 2008.

[81] C. Chapple, "Antimuscarinics in men with lower urinary tract symptoms suggestive of bladder outlet obstruction due to benign prostatic hyperplasia," *Current Opinion in Urology*, vol. 20, no. 1, pp. 43–48, 2010.

[82] C. Füllhase, R. Soler, C. Gratzke, M. Brodsky, G. J. Christ, and K. E. Andersson, "Urodynamic evaluation of fesoterodine metabolite, doxazosin and their combination in a rat model of partial urethral obstruction," *British Journal of Urology International*, vol. 106, no. 2, pp. 287–293, 2010.

[83] G. Conte-Santos, M. Rebbassa-Llull, L. Soriano-Burrull et al., "Study of safety and urodynamic characteriztion of treatment with tamsulosin, tolderodine and tamsulosin plus tolderodine, in men with LUTS," *European Urology*, vol. 8, no. 4, p. 237, 2009, abstract 468.

[84] B. T. Blake-James, A. Rashidian, Y. Ikeda, and M. Emberton, "The role of anticholinergics in men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia: a systematic review and meta-analysis," *British Journal of Urology International*, vol. 99, no. 1, pp. 85–96, 2007.

[85] G. Novara, A. Galfano, V. Ficarra, and W. Artibani, "Anticholinergic drugs in patients with bladder outlet obstruction and lower urinary tract symptoms: a systematic review," *European Urology*, vol. 50, no. 4, pp. 675–683, 2006.

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Review Article

Biomarkers in Overactive Bladder: A New Objective and Noninvasive Tool?

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Overactive bladder syndrome (OAB) is a highly prevalent urinary dysfunction, with considerable economic and human costs. Clinical diagnosis of OAB is still based on subjective symptoms. A new accurate, objective and noninvasive test to diagnose OAB and assess therapeutic outcome is lacking. Recent studies in lower urinary tract (LUT) dysfunctions, particularly in OAB patients, indicate that urinary proteins (neurotrophins, prostaglandins, and cytokines), serum C reactive protein, and detrusor wall thickness are altered, and such changes could be used as biomarkers of the disease. Nowadays, increasing emphasis has been given to the role of urinary neurotrophins, namely nerve growth factor (NGF) and brain derived neurotrophic factor (BDNF), as key players in some urinary dysfunctions. Although recently considered to be a bladder dysfunction biomarker, urinary NGF presents low sensitivity and specificity. Preliminary results suggest that BDNF may serve as a more efficient biomarker. Even though we have to wait for future studies to confirm the potential role of NGF and BDNF as OAB biomarkers, it is already clear that neurotrophins will contribute to elucidate the physiopathological basis of OAB. Herein are reviewed the latest advances in this new and exciting field, the detection and clinical application of emerging OAB biomarkers.

1. Introduction

OAB is currently recognized as a chronic disorder with an overall prevalence in the adult population of above 10%, but that may exceed 40% in elderly groups [1]. According to the International Continence Society (ICS), OAB is defined as a clinical syndrome characterized by the presence of urgency, with or without urgency incontinence, usually accompanied by daytime frequency and nocturia, in the absence of proven infection or other obvious pathology [2, 3]. Urinary urgency, defined as a sudden compelling desire to void that is difficult to defer, is the unique symptom that must be present in order to establish the diagnosis of OAB [3]. However, urgency is difficult to be understood by patients and caregivers. Differentiation between urgency and urge is not always straightforward. Yet, urge is a normal bladder sensation, gradual in appearance, usually proportional to the degree of bladder filling, and that can be easily controlled by individuals. In addition, grading urinary urgency is a difficult task, which may render difficult the efficacy of a therapy. The multiple questionnaires available to quantify and grade urgency severity (USS, OABq) reflect this problem [4, 5].

One way to overcome this problem would be the introduction of an objective test for the diagnosis of OAB. During the last few years, several attempts have been made, though with limited success. Detrusor overactivity (DO) is the urodynamic hallmark of OAB. Nevertheless, this abnormality can only be identified in half of the patients, whereas normal individuals often have asymptomatic involuntary detrusor contractions [6]. In addition, urodynamics is an invasive test. These facts decrease the role of this test as a useful tool for OAB diagnosis.

Another potential marker for OAB is detrusor wall thickness (DWT), determined by ultrasound. In patients with OAB, it has been hypothesized that frequent detrusor contractions during bladder filling result in tetanic detrusor motions and cause muscular hypertrophy. DWT is shown to be higher in OAB patients and to decrease in response to antimuscarinic treatment [7], suggesting that DWT measurement is a useful biomarker to monitor disease progression and therapeutic efficacy. However, DWT measurement may not be reproducible. Liu et al. determined DWT in normal subjects and patients with OAB dry, OAB wet and interstitial cystitis (IC). Wide variation was found among all groups. There was a trend to a higher DWT in patients with OAB, whether dry or wet, compared with normal controls and patients with IC. However, the difference was not statistical significant [7]. A recent study compared measurement of DWT by transvaginal and transabdominal ultrasound. No significant difference of transvaginal ultrasound measured DWT was noted among women with OAB dry, OAB wet, and normal controls. Inversely, transabdominally measured DWT, at bladder capacity, was significantly higher in women with OAB wet or DO [8]. Until now, studies are contradictory about the potential value of DWT as a diagnostic tool for OAB [9]. Similar problems have been detected with DWT measurement in patients with bladder outlet obstruction (BOO). Various studies showed an increase in DWT with increasing the degree of BOO and a predictive value of DWT in the diagnosis of BOO [10, 11]. In contrast, in a recent investigation, DWT was remarkably uniform whether patients had a normal urodynamic test, BOO, or DO [8]. The differences in the values of DWT obtained in various studies may be explained by the use of different ultrasound probes, with different frequencies, as well as in the resolution of ultrasound-generated images [8].

Recently, near-infrared spectroscopy (NIRS), an optical technology, has also been studied as a potential noninvasive, diagnostic tool for DO in OAB patients. NIRS detects the hemodynamic variations in tissues by the use of noninvasive measurements of changes in the concentration of tissue chromophores, such as oxyhemoglobin (O2Hb) and deoxyhemoglobin (HHb). Involuntary bladder contractions may cause changes detectable by NIRS [12]. Until now, its value to detect DO in clinical practice needs to be confirmed.

Taking into account the previous data, new simple, noninvasive tests to diagnose OAB and assess therapeutic outcome are eagerly needed. Some recent studies have focused on this new and exciting field, the detection and clinical application of OAB biomarkers.

2. Neurotrophins

Nowadays, increasing attention is given to the role of neurotrophins, namely, nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) in OAB. Neurotrophins are growth factors required by neuronal cells for differentiation, survival, and maintenance, with a broad range of activities in the central and peripheral nervous system either in the developing or in the adult mammal [13]. It has been suggested that NGF and BDNF are released from urothelial and detrusor smooth muscle cells. These neurotrophins act by binding to high-affinity receptors TrkA (for NGF) and TrkB (for BDNF), cell-surface transmembrane glycoproteins expressed in bladder urothelial cells, and primary afferents [13–15].

Low-affinity receptors, such as the p75, may also play an important role on neurotrophins effects, but this aspect is still poorly studied.

2.1. Urinary Nerve Growth Factor. NGF was the first neurotrophin to be discovered, by Rita Levi-Montalcini, in the 1950s [16]. It may be synthesized by both neuronal and nonneuronal cells and plays an essential role during the development of the peripheral nervous system, regulating the survival and function of postganglionic sympathetic neurons and small-diameter primary afferents [17–20]. Upon binding to TrkA, NGF may induce the expression of several genes coding for various neurotransmitters, receptors, and voltage-gated ion channels [17]. In addition to TrkA, NGF binds to p75, a low-affinity pan-neurotrophic receptor also expressed in bladder urothelial cells and primary afferent nerves. Several clinical and experimental data have suggested an interesting link between increased levels of NGF, either in bladder tissue or urine, and DO, and OAB [21]. In animal models, NGF is released in high amounts from smooth muscle cells and urothelium of overactive bladders [14]. In addition, recent studies have revealed that acute and chronic local administration of NGF reduces bladder capacity and intercontraction interval and increases bladder reflex contractions [22–25]. Likewise, TrkA blockade or NGF sequestration decreases the high frequency of bladder contractions in animal models of bladder inflammation [26] and spinal cord transection [27, 28]. Interestingly, TRPV1 seems to be an essential downstream receptor for NGF activity in the bladder. TRPV1 knockout mice, in contrast with wild-type littermates, do not develop DO, in spite of exogenous NGF administration [26]. Also, NGF increases TRPV1 translation and activity [29]. This crosstalk between NGF and TRP family should be further investigated in the future.

2.1.1. Urinary NGF Levels in OAB Patients. Similarly to what happens in experimental studies, in humans, it has also been postulated that increased levels of NGF in urine could sensitize bladder afferent pathways and enhance bladder sensory input arriving to the central nervous system, eventually leading to DO. Supporting this hypothesis, increased levels of NGF have been found in the urine of patients with OAB, idiopathic and neurogenic DO, IC, and BOO [30–36].

Recent pilot clinical studies have shown that urinary NGF levels are significantly higher (approximately 12-fold) in patients with OAB than in normal controls [37–40]. Urinary NGF concentrations have been found to be increased in patients with OAB, particularly in those complaining of urgency urinary incontinence (OAB wet) [39, 40]. Interestingly, it has also been found that urinary NGF concentration in OAB patients seems to correlate with urgency intensity. Liu and coworkers reported on that patients classified as having modified Indevus Urgency Severity Scale (USS) scores

of 3 or 4 had significantly higher NGF levels than those with a score of 2 or lower [40].

The sensitivity and specificity was recently evaluated. Using a urinary NGF/creatinine ratio >0.05, Chen and Kuo found that the sensitivity and specificity of this test in the diagnosis of OAB was 67.9% and 93.8%, respectively [41]. In spite of being a small study, recently, Antunes-Lopes et al. found lower values of sensitivity and specificity for NGF/creatinine ratio (>200 pg/mg), with an area under the curve in receiver-operator characteristics (ROCs) analysis of 0.68 (Figure 1) [42]. In this study, there was a trend to higher NGF/creatinine ratio in OAB patients compared to healthy volunteers, but the difference did not reach statistical significance [42]. Moreover, surprisingly, in OAB patients with high urinary concentration of NGF, Birder and coworkers did not find similar increases in bladder samples obtained from the same group of patients [43]. More studies are missing to clarify this puzzling discrepancy.

2.1.2. Urinary NGF as a Marker of Response to OAB Treatment? Antimuscarinic treatment was shown to diminish urinary NGF levels in parallel to the reduction of the USS score, with the reversal occurring upon withdrawal of the therapy [44, 45]. Also, in patients with intractable idiopathic and neurogenic DO, detrusor injection of onabotulinum toxin A has been shown to reduce urinary NGF levels [46]. According to these data, urinary NGF level could be used as a tool to monitor the therapeutic effect of antimuscarinics and detrusor BoNT-A injection in OAB. However, as these studies were not placebo controlled, some caution should be taken in the results interpretation.

2.2. Urinary Brain-Derived Neurotrophic Factor. BDNF is the most abundant neurotrophin in the human body, although our knowledge about its role in normal and pathological conditions is still very limited [47]. Like NGF, BDNF also contributes to the survival and normal function of sensory neurons [48–51]. BDNF is constitutively expressed by small and medium-sized peptidergic neurons, but it is also produced by nonneuronal cells [52, 53]. Besides its well-established trophic effect on neuronal tissue and its relevance in plasticity events, the importance of BDNF in nociception has also been established [54]. BDNF is present in the spinal cord, in terminal endings of sensory fibres, colocalizing with substance P and CGRP [55]. Interestingly, its expression may be regulated by NGF [17].

2.2.1. BDNF in Lower Urinary Tract Dysfunctions. Little is known about the role of BDNF in bladder function, both in normal and in pathological conditions, and available studies are mostly confined to experimental models of bladder dysfunction. It has been demonstrated that after chronic bladder inflammation or spinal cord injury, the synthesis of BDNF in the urinary bladder is strongly increased [56–58]. A recent study showed that BDNF sequestration improved bladder function in rats with chronic cystitis [59]. Nevertheless, BDNF sequestration did not produce any effects on bladder reflex activity of intact animals, suggesting that BDNF effect on bladder function is relevant only in pathological conditions.

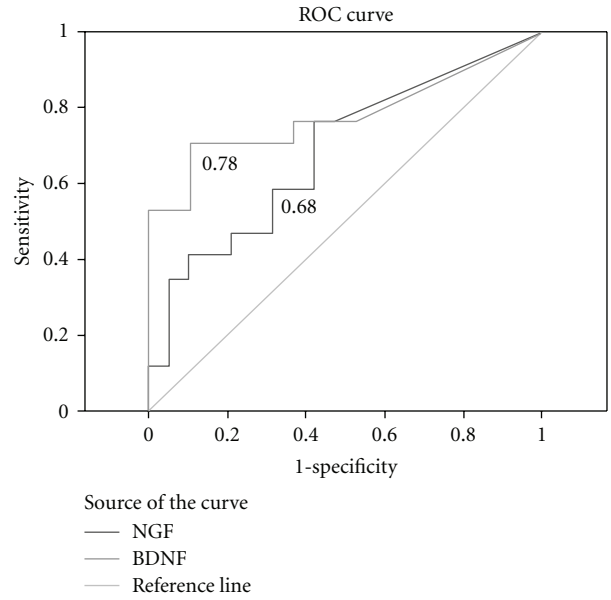

Figure 1: Receiver-operator characteristic (ROC) curves of urinary NGF/creatinine and urinary BDNF/creatinine in OAB patients. Notice that, for this cohort, BDNF has a better AUC than NGF.

In a recent study, Antunes-Lopes et al. assessed urinary levels of BDNF in a population of adult healthy volunteers (20 females and 20 males) to investigate if there was a physiological pattern of secretion and if there were differences between genders. In healthy volunteers, BDNF/creatinine ratio (pg/mg) was systematically low, irrespective of gender or time of urine sampling. In contrast, urinary BDNF/creatinine ratio was significantly higher in OAB patients compared to controls (Figure 2) [60].

Auspiciously, the striking differences found in this preliminary observational study between OAB patients and controls suggest that urinary BDNF may serve as a potential biomarker of OAB syndrome. Using ROC analysis, the area under the curve of urinary BDNF (Figure 1) seems to support this hypothesis, but further studies, involving other centers, are necessary before a solid statement can be created [60].

In addition to OAB, urinary BDNF was newly evaluated in the urine of bladder pain syndrome/IC patients. The urinary concentration was high at baseline and significantly reduced after botulinum toxin administration to the bladder trigone [35]. A positive correlation could be established between BDNF decrease and LUTS improvement [35].

2.3. Neurotrophins and Intracellular Pathways: Targets for New Therapies? The study of urinary NT in patients with OAB has provided new insights to the underlying physiopathology of this disorder. Inflammation in the urinary tract can cause an elevation of the urinary NGF level. Therefore, it can be suggested that OAB is an inflammatory disorder of the bladder [21]. NGF excretion is increased during bladder

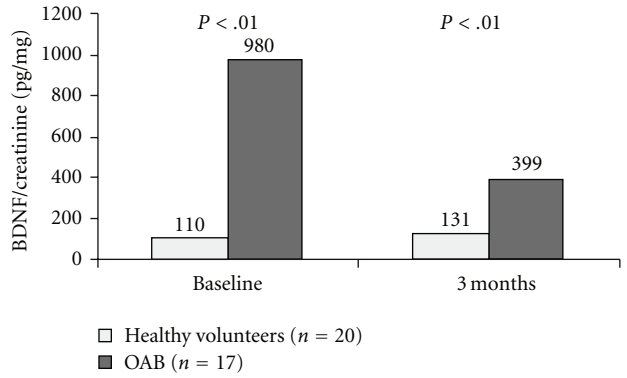

Figure 2: BDNF/creatinine in the urine of female healthy volunteers and OAB patients, at baseline and after 3 months of lifestyle intervention.

distension [36] although urinary NGF levels were augmented in patients with OAB, whether the urine was collected from an empty or a full distended bladder [61]. Although urinary NGF increases significantly in normal controls when they refer a strong desire to void NGF levels were significantly lower than in patients with OAB at first sensation of filling [61]. These results suggest that urinary NGF level increases physiologically in normal controls at strong desire to void, but raises pathologically in patients with OAB [61]. Although the precise mechanisms by which urinary NGF promotes DO and OAB are not yet defined, neurotrophins are known to influence expression and activity of receptors that modulate bladder function, like P2X3 and TRPV1 receptors. Cruz et al. showed that the latter is, in fact, essential for NGF-mediated DO [29]. This finding is important to envisage an effective strategy to counteract the consequences of high urinary NGF, levels in patients with DO [29]. In addition, neurotrophins activate intracellular signalling pathways important for micturition control, as the MAPK-ERK pathway. Some new molecules that are able to sequester NGF and other neurotrophins (e.g., BDNF) have already been tested with success in preclinical models of DO [59, 62]. In the future, it is likely that Trk antagonists or neurotrophin sequestering proteins may be eventually useful and effective treatments to control DO and OAB symptoms.

3. Prostaglandins

Prostaglandins (PGs) regulate LUT function. PGs are locally synthesized in the bladder muscle and urothelium and triggered by detrusor muscle stretch, bladder nerve stimulation, bladder mucosa damage, and inflammation [63]. PGs seem to contribute to the basal ton of the detrusor and to modulate the activity of bladder nerves. PGs are involved in micturition reflex by decreasing thresholds of the stimuli necessary to trigger bladder contraction through activation of the capsaicin-sensitive afferent nerves. Therefore, PGs can be related to bladder storage symptoms in patients with OAB [63]. In an experimental study in rats, intravesical instillation of PGE2 induced detrusor contraction, while its topical application to the urethra caused urethral relaxation [64]. Activation of prostaglandin EP3 receptors exerts an excitatory effect on urinary bladder function through modulation of bladder afferent pathways [65].

At a clinical level, Kim et al. found that urinary levels of PGE2 and PGF2α in patients with OAB were significantly increased compared to a control group [63]. In addition, an inverse correlation was found between urinary PGE2 and the volume to first desire to void and the maximum cystometric capacity [63]. On the other hand, Liu et al. measured urinary levels of PGE2 in patients with OAB wet, OAB dry, IC, and controls and did not find significant differences between the subgroups [66].

In summary, the role of urinary PGs in the diagnosis of OAB is still controversial and needs further investigation. Moreover, nonsteroidal anti-inflammatory drugs have shown little efficacy in treating OAB. A new alternative may be the blockade of PGE receptors. Molecules like ONO-8539, a PGE2 receptor subtype EP1 antagonist, entered recently in a phase 1 study [67], but it is still too soon to make clear statements about their therapeutic potential.

4. Urine Cytokines and Urine and Serum C-Reactive Protein

It has been hypothesized that OAB may be an inflammatory process of the bladder [68]. Supporting this theory, recent studies reported histological evidence of inflammation in bladder specimens from OAB patients [69, 70]. However, the biopsy-based confirmation of bladder inflammation in OAB requires an invasive and expensive procedure not exempted of morbidity. Alternatively, cytokines may represent a biomarker considering that they are elevated in biologic fluids during inflammation. In the particular case of OAB, Tyagi et al. analyzed the urine from OAB patients for selected cytokines, chemokines, growth factors, and soluble receptors. Their study revealed an elevation of several of these putative biomarkers in the urine of OAB patients ($P < .05$) [68]. Monocyte chemotactic protein-1 (MCP-1) and soluble fraction of the CD40 ligand (sCD40L) were increased more than tenfold over controls in the urine of OAB patients [68]. At least fivefold elevations were detected in the urinary levels of macrophage inflammatory protein (MIP-1β), IL-12p70/p40, IL-5, epidermal growth factor (EGF), and growth-related oncogene (GRO-α) in OAB patients compared to controls [68]. Finally, it was also noticed a threefold elevation in the urine levels of sIL-2Rα and IL-10 in the OAB group [68].

C-reactive protein (CRP) is a widely studied general marker of inflammation and infection. Its serum levels rise dramatically during inflammatory conditions and are used to determine disease progression or treatment effectiveness. Chuang et al. undertook a study to examine CRP levels serum, urine, and bladder tissue of OAB dry and OAB wet patients [71]. Significantly higher serum CRP levels were measured in OAB patients compared to controls [71]. Interestingly, higher values were noted in OAB wet than in OAB dry [71].

In what concerns urinary levels, the same study showed that urinary CRP was barely detectable and the mRNA expression of CRP in bladder biopsies was very modest [71]. Consequently, urinary and bladder CRPs seem to be much lower than serum CRP levels, and current available methods for detecting CRP might not be sensitive enough to develop a urinary assay. On the other hand, it should be reminded that serum CRP level in patients with LUT symptoms may not specifically reflect the condition of the LUT, as its levels are influenced by any systemic inflammatory condition [71, 72]. So, at this moment, the importance of CRP as an OAB biomarker seems rather modest.

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References

[1] D. E. Irwin, I. Milsom, S. Hunskaar et al., "Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC study," *European Urology*, vol. 50, no. 6, pp. 1306–1315, 2006.

[2] P. Abrams, L. Cardozo, M. Fall et al., "The standardisation of terminology of lower urinary tract function: report from the standardisation sub-committee of the international continence society," *Neurourology and Urodynamics*, vol. 21, no. 2, pp. 167–178, 2002.

[3] C. R. Chapple, W. Artibani, L. D. Cardozo et al., "The role of urinary urgency and its measurement in the overactive bladder symptom syndrome: current concepts and future prospects," *British Journal of Urology International*, vol. 95, no. 3, pp. 335–340, 2005.

[4] A. Nixon, S. Colman, L. Sabounjian et al., "A validated patient reported measure of urinary urgency severity in overactive bladder for use in clinical trials," *Journal of Urology*, vol. 174, no. 2, pp. 604–607, 2005.

[5] J. S. Starkman and R. R. Dmochowski, "Urgency assessment in the evaluation of overactive bladder (OAB)," *Neurourology and Urodynamics*, vol. 27, no. 1, pp. 13–21, 2008.

[6] H. Hashim and P. Abrams, "Is the bladder a reliable witness for predicting detrusor overactivity?" *Journal of Urology*, vol. 175, no. 1, pp. 191–195, 2006.

[7] H. T. Liu, M. B. Chancellor, and H. C. Kuo, "Decrease of urinary nerve growth factor levels after antimuscarinic therapy in patients with overactive bladder," *British Journal of Urology International*, vol. 103, no. 12, pp. 1668–1672, 2009.

[8] H. C. Kuo, "Measurement of detrusor wall thickness in women with overactive bladder by transvaginal and transabdominal sonography," *International Urogynecology Journal and Pelvic Floor Dysfunction*, vol. 20, no. 11, pp. 1293–1299, 2009.

[9] F. Cruz, J. Heesakkers, V. Khullar, and A. Tubaro, "Bladder wall thickness in overactive bladder: does it have a role?" *European Urology*, vol. 8, no. 9, supplement, pp. 769–771, 2009.

[10] M. Oelke, K. Höfner, U. Jonas, J. J. de la Rosette, D. T. Ubbink, and H. Wijkstra, "Diagnostic accuracy of noninvasive tests to evaluate bladder outlet obstruction in men: detrusor wall thickness, uroflowmetry, postvoid residual urine, and prostate volume," *European Urology*, vol. 52, no. 3, pp. 827–835, 2007.

[11] T. M. Kessler, R. Gerber, F. C. Burkhard, U. E. Studer, and H. Danuser, "Ultrasound assessment of detrusor thickness in men-can it predict bladder outlet obstruction and replace pressure flow study?" *Journal of Urology*, vol. 175, no. 6, pp. 2170–2173, 2006.

[12] F. F. Farag, F. M. Martens, K. W. D'Hauwers, W. F. Feitz, and J. P. Heesakkers, "Near-infrared spectroscopy: a novel, noninvasive, diagnostic method for detrusor overactivity in patients with overactive bladder symptoms—a preliminary and experimental study," *European Urology*, vol. 59, no. 5, pp. 757–762, 2011.

[13] S. J. Allen and D. Dawbarn, "Clinical relevance of the neurotrophins and their receptors," *Clinical Science*, vol. 110, no. 2, pp. 175–191, 2006.

[14] W. D. Steers and J. B. Tuttle, "Mechanisms of disease: the role of nerve growth factor in the pathophysiology of bladder disorders," *Nature Clinical Practice Urology*, vol. 3, no. 2, pp. 101–110, 2006.

[15] L. A. Birder and W. C. de Groat, "Mechanisms of disease: involvement of the urothelium in bladder dysfunction," *Nature Clinical Practice Urology*, vol. 4, no. 1, pp. 46–54, 2007.

[16] R. Levi-Montalcini, "Nerve growth factor," *Science*, vol. 187, no. 4172, p. 113, 1975.

[17] S. Pezet and S. B. McMahon, "Neurotrophins: mediators and modulators of pain," *Annual Review of Neuroscience*, vol. 29, pp. 507–538, 2006.

[18] D. H. Bennett, M. Koltzenburg, J. V. Priestley, D. L. Shelton, and S. B. McMahon, "Endogenous nerve growth factor regulates the sensitivity of nociceptors in the adult rat," *European Journal of Neuroscience*, vol. 10, no. 4, pp. 1282–1291, 1998.

[19] N. Dmitrieva, D. Shelton, A. S. C. Rice, and S. B. McMahon, "The role of nerve growth factor in a model of visceral inflammation," *Neuroscience*, vol. 78, no. 2, pp. 449–459, 1997.

[20] S. I. Jaggar, H. C. F. Scott, and A. S. C. Rice, "Inflammation of the rat urinary bladder is associated with a referred thermal hyperalgesia which is nerve growth factor dependent," *British Journal of Anaesthesia*, vol. 83, no. 3, pp. 442–448, 1999.

[21] H. C. Kuo, "Recent investigations of urinary nerve growth factor as a biomarker for overactive bladder syndrome," *Korean Journal of Urology*, vol. 50, no. 9, pp. 831–835, 2009.

[22] Y. C. Chuang, M. O. Fraser, Y. Yu, M. B. Chancellor, W. C. De Groat, and N. Yoshimura, "The role of bladder afferent pathways in bladder hyperactivity induced by the intravesical administration of nerve growth factor," *Journal of Urology*, vol. 165, no. 3, pp. 975–979, 2001.

[23] N. Yoshimura, N. E. Bennett, Y. Hayashi et al., "Bladder overactivity and hyperexcitability of bladder afferent neurons after intrathecal delivery of nerve growth factor in rats," *Journal of Neuroscience*, vol. 26, no. 42, pp. 10847–10855, 2006.

[24] K. Lamb, G. F. Gebhart, and K. Bielefeldt, "Increased nerve growth factor expression triggers bladder overactivity," *Journal of Pain*, vol. 5, no. 3, pp. 150–156, 2004.

[25] P. Zvara and M. A. Vizzard, "Exogenous overexpression of nerve growth factor in the urinary bladder produces bladder overactivity and altered micturition circuitry in the lumbosacral spinal cord," *BMC Physiology*, vol. 7, pp. 9–19, 2007.

[26] B. Frias, A. Charrua, R. Pinto et al., "Intrathecal blockade of Trk receptor and neurotrophins sequestration reduces pain and urinary frequency in an animal model of chronic bladder inflammation," *Neurourology and Urodynamics*, vol. 28, no. 7, pp. 708–708, 2009.

[27] S. Seki, K. Sasaki, M. O. Fraser et al., "Immunoneutralization of nerve growth factor in the lumbosacral spinal cord reduces bladder hyperreflexia in spinal cord injured rats," *Journal of Urology*, vol. 168, no. 5, pp. 2269–2274, 2002.

[28] S. Seki, K. Sasaki, Y. Igawa et al., "Suppression of detrusor-sphincter dyssynergia by immunoneutralization of nerve growth factor in lumbosacral spinal cord in spinal cord injured rats," *Journal of Urology*, vol. 171, no. 1, pp. 478–482, 2004.

[29] F. Cruz et al., "NGF-induced detrusor overactivity is TRPV1 dependent," *European Urology Supplements*, vol. 9, no. 2, p. 69, 2010.

[30] J. B. Tuttle, W. D. Steers, M. Albo, and E. Nataluk, "Neural input regulates tissue NGF and growth of the adult rat urinary bladder," *Journal of the Autonomic Nervous System*, vol. 49, no. 2, pp. 147–158, 1994.

[31] E. M. Lowe, P. Anand, G. Terenghi, R. E. Williams-Chestnut, D. V. Sinicropi, and J. L. Osborne, "Increased nerve growth factor levels in the urinary bladder of women with idiopathic sensory urgency and interstitial cystitis," *British Journal of Urology*, vol. 79, no. 4, pp. 572–577, 1997.

[32] M. C. Dupont, J. M. Spitsbergen, K. B. Kim, J. B. Tuttle, and W. D. Steers, "Histological and neurotrophic changes triggered by varying models of bladder inflammation," *Journal of Urology*, vol. 166, no. 3, pp. 1111–1118, 2001.

[33] M. A. Vizzard et al., "Neurochemical plasticity and the role of neurotrophic factors in bladder reflex pathways after spinal cord injury," *Progress in Brain Research*, vol. 152, pp. 97–115, 2006.

[34] H. T. Liu, A. B. Liu, M. B. Chancellor, and H. C. Kuo, "Urinary nerve growth factor level is correlated with the severity of neurological impairment in patients with cerebrovascular accident," *British Journal of Urology International*, vol. 104, no. 8, pp. 1158–1162, 2009.

[35] R. Pinto, T. Lopes, B. Frias et al., "Trigonal injection of botulinum toxin A in patients with refractory bladder pain syndrome/interstitial cystitis," *European Urology*, vol. 58, no. 3, pp. 360–365, 2010.

[36] W. D. Steers, S. Kolbeck, D. Creedon, and J. B. Tuttle, "Nerve growth factor in the urinary bladder of the adult regulates neuronal form and function," *Journal of Clinical Investigation*, vol. 88, no. 5, pp. 1709–1715, 1991.

[37] J. C. Kim, E. Y. Park, S. I. Seo, Y. H. Park, and T. K. Hwang, "Nerve growth factor and prostaglandins in the urine of female patients with overactive bladder," *Journal of Urology*, vol. 175, no. 5, pp. 1773–1776, 2006.

[38] T. Yokoyama, H. Kumon, and A. Nagai, "Correlation of urinary nerve growth factor level with pathogenesis of overactive bladder," *Neurourology and Urodynamics*, vol. 27, no. 5, pp. 417–420, 2008.

[39] H. T. Liu and H. C. Kuo, "Urinary nerve growth factor level could be a potential biomarker for diagnosis of overactive bladder," *Journal of Urology*, vol. 179, no. 6, pp. 2270–2274, 2008.

[40] H. T. Liu, C. Y. Chen, and H. C. Kuo, "Urinary nerve growth factor in women with overactive bladder syndrome," *British Journal of Urology International*, vol. 107, no. 5, pp. 799–803, 2011.

[41] C. Y. Chen and H. C. Kuo, "Novel urinary biomarkers in the diagnosis and assessment of overactive bladder," *Incontinence and Pelvic Floor Dysfunction*, vol. 3, no. 1, pp. 20–23, 2009.

[42] T. Antunes-Lopes et al., "Urinary neurotrophins—potential biomarkers of overactive bladder," *Journal of Urology*, vol. 185, no. 4S, pp. 780–781, 2011.

[43] L. A. Birder, A. Wolf-Johnston, D. Griffiths, and N. M. Resnick, "Role of urothelial nerve growth factor in human bladder function," *Neurourology and Urodynamics*, vol. 26, no. 3, pp. 405–409, 2007.

[44] H. T. Liu and H. C. Kuo, "Urinary nerve growth factor levels are increased in patients with bladder outlet obstruction with overactive bladder symptoms and reduced after successful medical treatment," *Urology*, vol. 72, no. 1, pp. 104–108, 2008.

[45] H. T. Liu, M. B. Chancellor, and H. C. Kuo, "Decrease of urinary nerve growth factor levels after antimuscarinic therapy in patients with overactive bladder," *British Journal of Urology International*, vol. 103, no. 12, pp. 1668–1672, 2009.

[46] H. T. Liu, M. B. Chancellor, and H. C. Kuo, "Urinary nerve growth factor levels are elevated in patients with detrusor overactivity and decreased in responders to detrusor botulinum toxin-A injection," *European Urology*, vol. 56, no. 4, pp. 700–707, 2009.

[47] S. Pezet, M. Malcangio, and S. B. McMahon, "BDNF: a neuromodulator in nociceptive pathways?" *Brain Research Reviews*, vol. 40, no. 1-3, pp. 240–249, 2002.

[48] B. J. Kerr, E. J. Bradbury, D. L. H. Bennett et al., "Brain-derived neurotrophic factor modulates nociceptive sensory inputs and NMDA-evoked responses in the rat spinal cord," *Journal of Neuroscience*, vol. 19, no. 12, pp. 5138–5148, 1999.

[49] A. Merighi, C. Salio, A. Ghirri et al., "BDNF as a pain modulator," *Progress in Neurobiology*, vol. 85, no. 3, pp. 297–317, 2008.

[50] G. J. Michael, S. Averill, A. Nitkunan et al., "Nerve growth factor treatment increases brain-derived neurotrophic factor selectively in TrkA-expressing dorsal root ganglion cells and in their central terminations within the spinal cord," *Journal of Neuroscience*, vol. 17, no. 21, pp. 8476–8490, 1997.

[51] D. Hellard, T. Brosenitsch, B. Fritzsch, and D. M. Katz, "Cranial sensory neuron development in the absence of brain-derived neurotrophic factor in BDNF/Bax double null mice," *Developmental Biology*, vol. 275, no. 1, pp. 34–43, 2004.

[52] K. Obata and K. Noguchi, "BDNF in sensory neurons and chronic pain," *Neuroscience Research*, vol. 55, no. 1, pp. 1–10, 2006.

[53] X. F. Zhou and R. A. Rush, "Endogenous brain-derived neurotrophic factor is anterogradely transported in primary sensory neurons," *Neuroscience*, vol. 74, no. 4, pp. 945–951, 1996.

[54] J. Zhao, A. Seereeram, M. A. Nassar et al., "Nociceptor-derived brain-derived neurotrophic factor regulates acute and inflammatory but not neuropathic pain," *Molecular and Cellular Neuroscience*, vol. 31, no. 3, pp. 539–548, 2006.

[55] A. Merighi, G. Carmignoto, S. Gobbo et al., "Neurotrophins in spinal cord nociceptive pathways," *Progress in Brain Research*, vol. 146, pp. 291–321, 2004.

[56] L. Y. Qiao and M. A. Vizzard, "Cystitis-induced upregulation of tyrosine kinase (TrkA, TrkB) receptor expression and phosphorylation in rat micturition pathways," *Journal of Comparative Neurology*, vol. 454, no. 2, pp. 200–211, 2002.

[57] L. Qiao and M. A. Vizzard, "Up-regulation of tyrosine kinase (Trka, Trkb) receptor expression and phosphorylation in lumbosacral dorsal root ganglia after chronic spinal cord (T8-T10) injury," *Journal of Comparative Neurology*, vol. 449, no. 3, pp. 217–230, 2002.

[58] L. Y. Qiao and M. A. Vizzard, "Spinal cord injury-induced expression of TrkA, TrkB, phosphorylated CREB, and c-Jun in rat lumbosacral dorsal root ganglia," *Journal of Comparative Neurology*, vol. 482, no. 2, pp. 142–154, 2005.

[59] R. Pinto, B. Frias, S. Allen et al., "Sequestration of brain derived nerve factor by intravenous delivery of TrkB-Ig2 reduces bladder overactivity and noxious input in animals with chronic cystitis," *Neuroscience*, vol. 166, no. 3, pp. 907–916, 2010.

[60] T. Antunes-Lopes et al., "Urinary levels of brain derived neurotrophic factor (BDNF) in women with overactive bladder (OAB) syndrome correlate with the severity of symptoms," *European Urology Supplements*, vol. 10, no. 2, pp. 277–278, 2011.

[61] H. T. Liu and H. C. Kuo, "Urinary nerve growth factor levels are elevated in patients with overactive bladder and do not significantly increase with bladder distention," *Neurourology and Urodynamics*, vol. 28, no. 1, pp. 78–81, 2009.

[62] V. Y. Hu, P. Zvara, A. Dattilio et al., "Decrease in bladder overactivity with REN1820 in rats with cyclophosphamide induced cystitis," *Journal of Urology*, vol. 173, no. 3, pp. 1016–1021, 2005.

[63] J. C. Kim, E. Y. Park, S. I. Seo, Y. H. Park, and T. K. Hwang, "Nerve growth factor and prostaglandins in the urine of female patients with overactive bladder," *Journal of Urology*, vol. 175, no. 5, pp. 1773–1776, 2006.

[64] O. Yokoyama, Y. Miwa, N. Oyama, Y. Aoki, H. Ito, and H. Akino, "Antimuscarinic drug inhibits detrusor overactivity induced by topical application of prostaglandin E2 to the urethra with a decrease in urethral pressure," *Journal of Urology*, vol. 178, no. 5, pp. 2208–2212, 2007.

[65] X. Su, L. A. Leon, C. W. Wu et al., "Modulation of bladder function by prostaglandin EP3 receptors in the central nervous system," *American Journal of Physiology*, vol. 295, no. 4, pp. F984–F994, 2008.

[66] H. T. Liu, P. Tyagi, M. B. Chancellor, and H. C. Kuo, "Urinary nerve growth factor but not prostaglandin E2 increases in patients with interstitial cystitis/bladder pain syndrome and detrusor overactivity," *British Journal of Urology International*, vol. 106, no. 11, pp. 1681–1685, 2010.

[67] D. Wilbraham, T. Masuda, S. Deacon, R. Kuwayama, and S. Vincent, "Safety, tolerability, and pharmacokinetic of multiple ascending doses of the EP-1 receptor antagonist ONO-8539, a potential new and novel therapy to overactive bladder in healthy young and elderly subjects," *European Urology Supplements*, vol. 9, no. 2, p. 250, 2010.

[68] P. Tyagi, D. Barclay, R. Zamora et al., "Urine cytokines suggest an inflammatory response in the overactive bladder: a pilot study," *International Urology and Nephrology*, vol. 42, no. 3, pp. 629–635, 2010.

[69] E. Compérat, A. Reitz, A. Delcourt, F. Capron, P. Denys, and E. Chartier-Kastler, "Histologic features in the urinary bladder wall affected from neurogenic overactivity-a comparison of inflammation, oedema and fibrosis with and without injection of botulinum toxin type A," *European Urology*, vol. 50, no. 5, pp. 1058–1064, 2006.

[70] A. Apostolidis, T. S. Jacques, A. Freeman et al., "Histological changes in the urothelium and suburothelium of human overactive bladder following intradetrusor injections of botulinum neurotoxin type A for the treatment of neurogenic or idiopathic detrusor overactivity," *European Urology*, vol. 53, no. 6, pp. 1245–1253, 2008.

[71] Y. C. Chuang, V. Tyagi, R. T. Liu, and M. B. Chancellor, "Urine and serum C-reactive protein levels as potential biomarkers of lower urinary tract symptoms," *Urological Science*, vol. 21, no. 3, pp. 132–136, 2010.

[72] V. Kupelian, K. T. McVary, M. J. Barry et al., "Association of C-reactive protein (CPR) and lower urinary tract symptoms in men and women: results from boston area community health survey," *Urology*, vol. 73, no. 5, pp. 950–957, 2009.

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Review Article

Pelvic Electrical Neuromodulation for the Treatment of Overactive Bladder Symptoms

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Overactive bladder syndrome negatively affects the daily life of many people. First-line conservative treatments, such as antimuscarinics, do not always lead to sufficient improvement of the complaints and/or are often associated with disabling adverse effects leading to treatment failure. Electrical stimulation of the sacral nerves has emerged as an alternative and attractive treatment for refractory cases of bladder overactivity. Few theories attempted to explain its mechanism of action which remains elusive. It involves percutaneous posterior tibial nerve stimulation and more commonly sacral neuromodulation. For the latter, temporary sacral nerve stimulation is the first step. If the test stimulation is successful, a permanent device is implanted. The procedure is safe and reversible. It carries a durable success rate. The technique should be combined with careful followup and attentive adjustments of the stimulation parameters in order to optimize the clinical outcomes. This paper provides a review on the indications, possible mechanisms of action, surgical aspects and possible complications, and safety issues of this technique. The efficacy of the technique is also addressed.

1. Introduction

Overactive bladder (OAB) also referred to as the urgency-frequency syndrome, with or without urge urinary incontinence, can considerably impair the patient's quality of life. It is widely accepted that diet and life style modifications, behavioural therapy, and medication belong to the standard conservative therapeutic options and are considered as first-line measures. The International Consultation on Incontinence (ICI) guidelines states that when the first-line approach is not fully satisfactory or fails after 8–12 weeks, alternative therapies should be sought out [1]. It is worthwhile and justified to proceed to second-line therapy if patients are refractory to antimuscarinic therapy or if the treatment is contraindicated. Second-line therapies include less invasive measures such as detrusor injections with botulinum toxin (BTX) and sacral neuromodulation (SNM), whereas more invasive measures constitute surgical techniques, for example, bladder augmentation or substitution. Pelvic neuromodulation has been proven effective and is today an established treatment option for patients refractory to or intolerant of conservative treatments. It involves percutaneous posterior tibial nerve stimulation (PTNS) and more commonly SNM. This paper provides a contemporary overview of pelvic neuromodulation addressing mechanism of action, surgical and technical aspects, and safety and clinical outcomes with special emphasis on SNM.

2. Electrical Neuromodulation

In the settings of OAB, electrical neuromodulation devices act to modulate detrusor contractions. The use of neuromodulation is based on the knowledge that urge incontinence usually results from an imbalance of inhibitory and excitatory control systems, often causing a "hyperactive" detrusor, leading to incontinence during the filling phase [2]. In 1977, Teague and Merrill transrectally stimulated the pudendal nerve electrically in dogs which was found to activate pudendal-to-pelvic nerve reflex that depresses or eliminates uninhibited detrusor contractions [3]. Tai et al. were able to show the effectiveness of S2 sacral spinal

cord microstimulation with a single electrode to induce prominent bladder and urethral sphincter responses in spinal cord-injured cats demonstrating the potential for using microstimulation techniques to modulate lower urinary tract function in patients with neurogenic voiding dysfunctions [4]. Another publication by the same group showed that in anesthetized chronic spinal cord-injured cats, impaired storage and voiding functions of the lower urinary tract could be improved by activation of the somatic afferent pathways in the pudendal nerve [5]. The authors demonstrated that electrical stimulation of the pudendal nerve at 3 Hz inhibited nonvoiding contractions during bladder filling, suppressed reflex voiding, and increased bladder capacity. In a human study, data of 22 patients with OAB, who underwent an ambulant urodynamic investigations (ACM) before and during SNM, were investigated by Scheepens et al. [6]. Blind analysis of the ACM was performed, and the detrusor activity index (DAI) was calculated as the degree of detrusor overactivity. The subjective as well as the objective results showed a decrease in bladder overactivity during SNM. During SNM, instabilities of bladder were still present; however, bladder overactivity was reduced. A significant correlation was found in DAI reduction of the ACM before and during SNM as compared to the clinical improvement on OAB symptoms.

This concept has become popular since it bridges the gap between conservative treatment and highly invasive options. Currently, these devices include SNM via surgically implanted electrodes and newer methods that deliver percutaneous stimulation of the peripheral tibial nerve. The exact mechanism of action is not well understood. A number of theories have been proposed to explain the effect of electrical neuromodulation which can be summarized as follows.

(i) In human subjects, it was shown that sensory input through the pudendal nerve inhibited detrusor activity and, therefore, pudendal nerve stimulation and enhancement of external sphincter tone may serve to control bladder overactivity and facilitate urine storage [7].

(ii) The bladder tends to respond to neural stimulation initially with rapid contraction followed by slow, longer-lasting relaxation. With recurrent, repetitive stimuli produced by the electrical stimulation, there is a decay and downregulation of the bladder's response, thus reducing the detrusor muscle overactivity [8].

(iii) Stimulation of afferent sacral nerves in either the pelvis or lower extremities increases the inhibitory stimuli to the efferent pelvic nerve and reduces detrusor contractility. One theory is that there is supraspinal inhibition of the detrusor [2]. Another assumption is that, at low bladder volumes, there is stimulation of the hypogastric nerve through activation of sympathetic fibers and at maximal bladder volume direct stimulation of the pudendal nerve nuclei in the spinal cord [9, 10].

(iv) It is assumed that neuromodulation affects the "neuroaxis" at various levels and restores the balance between excitatory and inhibitory regulation at various locations within the peripheral and central nervous system [11].

2.1. Percutaneous Posterior Tibial Nerve Stimulation (PTNS). PTNS is a minimally invasive, office-based procedure that involves percutaneous placement of a 34-gauge (ga) needle over the medial malleolus of the ankle with subchronic electrical stimulation of the posterior tibial nerve. The procedure is a 30-minute treatment session administered over a period of 12 weeks. Another method that has been described is implanting the device in the same area as well [12]. The procedure utilizes the peroneal nerve for transcutaneous access to the S3 spinal cord region.

PTNS has shown some promise in the treatment of patients with refractory urge incontinence. McGuire et al. originally reported the first study applying PTNS in 1983 [13]. Of 22 patients with urge incontinence, 55% were cured and 32% improved. Earlier data with PTNS show excellent success rates with approximately 50% of patients showing some response with few complications noticed, albeit in low-quality studies [14]. Recently, Yoong et al. described a shortened 6-week treatment protocol with PTNS in 43 women with refractory OAB [15]. The authors showed a significant reduction in symptoms and improvement in health-related quality of life suggesting that the duration of treatment can be halved compared with the conventional 12 weeks, which would make it more acceptable and cost effective for patients. In a slightly older study from Turkey, Kabay et al. demonstrated that 12 weeks of PTNS was effective to suppress neurogenic detrusor overactivity in 19 multiple sclerosis patients [16]. Although this is a promising technology, the results of one multicenter randomized trial of 100 patients with OAB symptoms did not show a reduced rate of urinary frequency when PTNS was compared to tolterodine extended release, 4 mg daily [17]. The technique is likely to have limited applicability due to response durability since it requires regularly applying a stimulus with a percutaneous needle.

2.2. Sacral Neuromodulation (SNM). SNM uses mild electrical pulses to activate or inhibit neural reflexes by continuously stimulating the sacral nerves that innervate the pelvic floor and lower urinary tract; it is also referred to as the pacemaker for the bladder. The technique was pioneered by Schmidt et al. at the University of California in San Francisco who introduced it in 1979 [18]. This was followed by further solidity by the same investigators in the mid-1980s [19, 20]. From the first experimental use of SNM in dogs, InterStimTM therapy was developed by Medtronic (Minneapolis, Minn, USA) for use in humans. This therapy employs an implanted unilateral lead stimulating the S3 nerve root that is attached to a small pacemaker placed within a subdermal pocket in the buttock region. It is FDA approved for refractory urge incontinence, refractory urgency frequency, and idiopathic nonobstructive urinary

retention. For application in OAB, the ICI level of recommendation is grade A for women and B for men [1]. The technique has been also used for conditions such as interstitial cystitis and pelvic pain syndrome. InterStim therapy has continuously evolved in terms of knowledge of its mode of action as well as in technical and surgical aspects. During the early stages of SNM, the permanent lead placement was secured by fascial fixation with the patient under general anaesthesia. However, Spinelli at al. developed a refined fixation method with twist locks or silicone anchors allowed a smaller incision under conscious sedation and, as such, a less invasive approach [21]. To further improve the technical features of the lead, Spinelli et al. designed a self-anchoring tined lead which compromises four sets of silicone tines proximal to the electrodes as an integral part of the lead body, with each tine element consisting of four flexible, pliant tines [22]. The system engages subcutaneous tissue, particularly muscle tissue, to decrease axial movement of the lead and consequent dislodgment of the stimulating electrodes. The tined lead obtained FDA approval in 2002 and opened gates for widespread application of SNM.

Preprocedure patient counselling is critical in reassuring the patient and managing treatment expectations. Once it has been decided that the patient is an appropriate candidate for InterStim therapy, implantation proceeds in 2 steps: a test phase and implantation or lead removal based on test response. The initial test phase can be performed in the office or operating room allowing for placement of the lead with a test period of 1 to 2 weeks; full implantation can be performed under local or general anesthesia. Patients are counselled that approximately 60% of patients undergoing office-based test stimulation and 70% undergoing operating room-based test stimulation will have a positive test response [23]. Response is objectively evaluated by pre- and postvoiding diaries assessing various urinary parameters.

2.2.1. One-Stage Implant. In the 1990s, Schmidt et al. devised a simple outpatient diagnostic test that involved percutaneous placement of a wire to stimulate the S3 nerve root and evaluate motor and sensory responses [24]. The innovative technique allowed for subchronic S3 nerve root stimulation, and this peripheral nerve evaluation (PNE) served as the basis for future clinical applications of SNM. In PNE, an insulated thin wire is placed into the third sacral nerve (S3) foramen in the vicinity of S3 with the patient under local anesthesia while placed on a table in the prone position. In our center, we utilize 1% plain lidocaine. The surgeon must make sure not to inject the local anesthetic into the foramen since this may lead to numbness of the underlying nerves that can preclude the desired sensory response. The sciatic notches can be palpated either uni- or bilaterally. The S3 foramen can be found one fingerbreadth off the midline at the level of the sciatic notch. The procedure is done bilaterally, and the side giving better response is chosen. Responses signalling correct placement include bellows contraction of the pelvic floor and plantar flexion of the great toe. With the in-office test stimulation, the patient will also be able to confirm correct placement with contraction or tingling of the pelvic floor muscles (e.g., rectum, vagina, scrotum, and perineum). S2 placement will demonstrate plantar flexion of the entire foot with lateral rotation, whereas S4 placement will reveal no lower extremity movement despite bellows response. Once the appropriate side and position selected, the temporary unipolar lead is connected to an external neurostimulator (external pulse generator) and taped to the skin surface. This procedure may be facilitated by the availability of office-based fluoroscopy. Response is assessed by pre- and postprocedure voiding diaries. Patients who respond favorably and demonstrate a 50% symptom improvement from baseline proceed to removal of the temporary lead followed by implantation of a quadripolar permanent lead and implantable neurostimulator placement. The leads are easily removed in the office once the test phase is complete, typically in 5 to 7 days. The duration of this test is limited to a maximum of 2 weeks because longer implantation of the temporary lead may increase the probability of bacterial contamination of the test stimulation lead [25]. Significant restrictions, such as no showering and decreased activities, also dictate short-term testing. Ideal candidates should not be obese, should have OAB without voiding dysfunction, and should not have any significant coexisting medical conditions that would make an office-based procedure difficult [23]. In addition, patients with previous sacral or coccygeal scar may not be ideal candidates since this may preclude localization and placement of the any components of the temporarily device.

Limitations of this approach include migration of the temporary wires and a suboptimal test phase, as well as the potential discrepancy in clinical response when the permanent quadripolar lead is implanted. Short-term testing period as well as the lead migration probably explain the relatively low success rate of PNE, estimated at around 50% [26, 27]. Another observation is that to 33% of the patients who have a beneficial test stimulation with a temporary lead do not continue to have a successful outcome after the INS is implanted or, in other words, are false-positive responders [28]. Exchange of leads during the one-stage implant procedure may contribute to therapy failure during followup [29]. On the other hand, some patients who do not respond to PNE may in fact have an excellent outcome when the permanent electrode and neurostimulator/implantable pulse generator (IPG) are implanted [30]. Lead migration is considered the main factor leading to false-negative results [28].

2.2.2. Two-Stage Implant. If the patient is not a candidate for office-based test stimulation or did not respond to the in-office test, test stimulation may be performed in the operating room (OR). Furthermore, the shift from PNE (one-stage implant) to a two-stage procedure helps to minimize technical-related failures and increase test efficacy and patient selection. Immediate implantation of a permanent lead aims to avoid lead migration and allows prolonged patient testing/screening [31, 32].

This procedure is similar to the office-based test but involves tined quadripolar leads, thus improving lead fixation and test response, and can be performed using intravenous (IV) sedation, local anaesthesia, or general anaesthesia. In case general anaesthesia is used, the anaesthetist is reminded to avoid using any long-acting muscle relaxants that may impair the ability to stimulate the sacral nerves or visualize their motor response. Fluoroscopy with C-arm should be utilized to facilitate placement. Once the right or left S3 foramen has been identified and subsequently chosen, the permanent tined lead is passed through the foramen needle. The lead is then exposed and tested in the 0, 1, 2, and 3 positions for response. Then, the sheath is carefully removed so as not to move the lead and expansion of the tines fix the lead in place. The lead is then tunnelled deeply through the subcutaneous fat to a position in the right or left buttock depending on the patient's dominant hand side where the permanent implantable pulse generator (IPG) will be placed eventually during the second stage. The lead is attached to the temporary connector and then tunneled through the subcutaneous fat to an alternative exit site. This is particularly an important step because if the patient were to get a superficial skin infection, then alternative exit site would help prevent the infection from spreading to the location of the permanent IPG and back to the lead [23]. Finally, the lead is connected to an external pulse generator and taped to the skin surface. A 7- to 14-day subchronic home test period is used to determine which patients meet criteria to have the IPG implanted. At the end of the test period, the patient returns to the OR for either removal of the lead or implantation of the IPG, depending on the subjective and objective responses.

A prospective, randomized study showed that the two-stage implant technique of SNM has a higher success rate compared to the one-stage method, despite prior positive PNE, both in the short term and in the long term [28]. Another important study by Borawski et al. randomized 17 patients to staged implant and 13 patients to PNE [26]. The staged implant group was significantly more likely to proceed to IPG implant than the PNE group (88% versus 46%). Similar results were shown by Peters et al. who also noted that sensory response assessment at the time of implantation reduced the reoperation rate from 43% to 0% [27]. In addition, increased response rate to SNM was noted when the testing period was extended from 5 to 7 days to 14 days per implanted electrode lead [31]. The costs for the test protocol with the tined leads are much higher compared to the PNE test. Currently, the use of either one of the two screening options is arbitrary.

2.2.3. Implantation. After a successful test phase, the patient is brought to the OR for implantation of the implantable generator (IPG). If the first test stimulation was office based, fluoroscopy is required to place the permanent lead. The quadripolar tined lead is inserted in a similar fashion on the side where the patient had the best in-office test response. The lead is then tunnelled deeply through the subcutaneous fat to an incision in the right or left buttock region. It is attached to the IPG and buried in the deep subcutaneous pocket. On the other hand, if the first phase was done in the OR and there is pre-existing placement of the permanent quadripolar lead, the implant stage is quick, does not require fluoroscopy, and can be performed under local or general anaesthesia. The previous incision where the temporary connector was placed in the buttock is opened, and the permanent IPG is then connected to the lead and buried in a deep subcutaneous pocket in the buttock. Buttock placement of the IPG has become an attractive alternative to subcutaneous implant in the lower part of the anterior abdominal wall because of the lower incidence of adverse events (approximately 2-fold), shorter operation time, and avoidance of patient repositioning during the operation [33]. Postoperatively, the IPG is switched on, and it is programmed with different electrodes mapping to give the patient a comfortable electrical stimulation. Patients need lifelong surveillance to manage device-related issues that may arise.

2.2.4. Complications, Safety, and Clinical Results. The very nature of this mode of therapy mandates a 100% reoperation to replace the IPG at some point due to the limited longevity of the neurostimulator. Adverse events are usually related to the implant procedure and the presence of the implant or of undesirable stimulation. The most common adverse events include lead migration, implant site pain, bowel dysfunction, and infection. The majority of adverse events do not require surgical intervention. Potential lead migration can be simply resolved without significant morbidity in the majority of patients by reprogramming, reinforcing the lead, or inserting a new lead contralaterally [34]. Some patients lose benefit due to accommodation to the stimulation, but contralateral placement can be attempted to overcome this [35]. If infection is superficial, the usual management is antibiotics; however, if there is a deep infection that is not resolved with oral or IV antibiotics, then explantation of the neurostimulator is required. In case of adverse stimulation, it is commonly sufficient to change the stimulation factors (e.g., electrode mapping, pulse width, amplitude, mode, or polarity). Hijaz et al. reported a review of complication management and implant troubleshooting strategy from the Cleveland Clinic database of 214 tine lead implants [36]. One hundred and sixty-one patients (75.5%) proceeded to placement of the IPG. Seventeen patients (10.5%) had the device completely removed for infection and failure of clinical response. Twenty-six patients (16.1%) underwent device revision due to attenuation of response, infection, pain at IPG site, and lead migration. The majority of patients with revision due to poor response had abnormal impedance measurements, with equalization of impedance in 2 leads being the most common finding. As a result, the authors strongly advocate IPG interrogation with impedance testing to completely evaluate patients with response-related dysfunction.

Contraindications for the patient with an implanted device include shortwave diathermy, microwave diathermy,

or therapeutic ultrasound diathermy. The diathermy's energy can be transferred through the implant and could be harmful. MRI is not recommended. Nevertheless, Elkelini and Hassouna reported on six patients with implanted sacral nerve stimulator who underwent eight MRI examinations at 1.5 Tesla conducted in areas outside the pelvis [37]. IPGs were examined before and after MRI procedures. All patients had their parameters recorded; then the IPGs were put to "nominal" status. Patients were monitored continuously during and after the procedure. During the MRI session, no patient showed symptoms that required stopping the examination. There was no change in perception of the stimulation after reprogramming of the implanted sacral nerve stimulator, according to patients' feedback. Devices were functioning properly, and no change in bladder functions was reported after MRI examinations. Another safety issue with SNM has been its effect in pregnant women and the developing fetuses. Wiseman and colleagues have addressed this issue by examining 6 eligible patients having SNM sacral who subsequently achieved pregnancy [38]. In 5 patients, the stimulator was deactivated between weeks 3 and 9 of gestation, after which 2 with a history of urinary retention had urinary tract infection. In another case, stimulation was discontinued 2 weeks before conception. The only noted complication developed in a pregnancy in which birth was premature at 34 weeks. Three patients underwent normal vaginal delivery, including 1 in whom subsequent implant reactivation did not resolve voiding dysfunction. In 3 cases, elective cesarean section was performed. All neonates were healthy. The authors concluded that when a patient on neuromodulation achieves pregnancy, the stimulation should be deactivated. If implant deactivation leads to urinary-related complications that threaten the pregnancy, reactivation should be considered. Elective cesarean section should be considered since it is possible for sacral lead damage or displacement to occur during vaginal delivery.

Several investigators have attempted to identify parameters that have predictive value in selecting the best candidates and those patients most likely to benefit from SNM therapy. Amundsen at al. reported that age >55 years and more than three chronic conditions were independent factors associated with a lower cure rate in patients implanted with a sacral neuromodulator for refractory urge incontinence [39]. They also noted that a neurologic condition may be associated with a decrease in the cure rate. Sherman et al. showed that evidence of pelvic muscle activity and test stimulation performed within 4 years were predictive factors of a positive response [40]. Other studies have demonstrated that patients with OAB symptoms and concomitant emotional disorders are far more likely to respond poorly to test stimulation, have symptom recrudescence following permanent implant, and have a higher incidence of reoperations [28, 41]. In a different study, Foster et al. showed that the reduction in 24-hour pad weight best predicted long-term patient satisfaction with SNM therapy [42].

There is convincing evidence for the success of SNM with the Interstim technique for refractory OAB. Several studies including RCTs and long-term observational studies reported fair clinical response between 64 and 88% of all patients [43]. All parameters investigated showed significant improvement compared to the placebo group: a 23–46% decrease in the number of voids per day, 44–77% increase in the average voided volume, 56–90% decrease in incontinence episodes per day, 64–100% decrease in pads, and 39% increase in maximum cystometric capacity [36, 41, 44–49]. Cappellano et al. showed a significant improvement in the quality of life score in patients with urgency incontinence who underwent SNM [50]. When followed up for 18 months, they were asked whether they would undergo this treatment again. 90% responded yes and 100% would recommend it to a relative or friend. Recently, Chartier-Kastler et al. published a multicenter prospective observational trial evaluating long-term effectiveness of SNM in patients with a permanent implant (2003–2009) [51]. Clinical improvement of greater than or equal to 50% was seen in 447/527 patients with OAB at 12 months followup. Clinical improvement remained relatively stable up to 60 months. Median patient satisfaction with treatment was between 60 and 80%. In another study, Leong et al. surveyed all patients who received SNM between 1990 and 2007 by mailing a questionnaire regarding satisfaction and experiences with the system [52]. Of the 275 questionnaires sent, 207 were returned for a 75% response rate. Treatment was done for OAB in 55% of the patients. Overall satisfaction with SNM was high at 90%.

Recently, several technical aspects of SNM with InterStim therapy led to the development of the InterStim II system, which received regulatory approval in Europe and the United States in 2006. InterStim II eliminates the need for extension cables and is almost 50% lighter and smaller in volume compared to the initial model. Subsequently, this allows for a smaller incision and smaller pocket to be created and thus less patient discomfort with higher patient acceptance which is of particular importance for skinny patients. However, the above-mentioned advantages come with the expense of a shorter battery life. Most new implanted IPGs are supplied with small iCon patient programmers, offering the patients the possibility to choose from up to four preset programs, provided better control of stimulation by the patient. Other available SNM technology includes the twin-chamber IPGs that can feed two electrodes providing synergetic effect.

3. Conclusions

Electrical neuromodulation devices act to modulate detrusor contractions. Currently, these devices include SNM and PTNS. SNM is an effective treatment modality for patients with refractory OAB and should be offered before applying more invasive, irreversible treatments. The procedure is safe and minimally invasive involving one or two-stage implantation. It carries small, treatable, and nonpermanent side effects. Although the mechanisms behind its action are still not fully understood, the therapy has been shown to be effective in the long term. Followup should include regular checks to determine efficacy of the therapy and a review of the electrical system. The SNM technology continues to evolve.

References

[1] P. Abrams, K. E. Andersson, L. Birder et al., *4th International Consultation on Incontinence. Recommendations of the International Scientific Committee: Evaluation and Treatment of Urinary Incontinence, Pelvic Organ Prolapse and Faecal Incontinence*, Health Publication Ltd, Paris, France, 4th edition, 2009.

[2] M. Fall and S. Lindstrom, "Electrical stimulation: a physiologic approach to the treatment of urinary incontinence," *Urologic Clinics of North America*, vol. 18, no. 2, pp. 393–407, 1991.

[3] C. T. Teague and D. C. Merrill, "Electric pelvic floor stimulation: mechanism of action," *Investigative Urology*, vol. 15, no. 1, pp. 65–69, 1977.

[4] C. Tai, A. M. Booth, W. C. De Groat, and J. R. Roppolo, "Bladder and urethral sphincter responses evoked by microstimulation of S2 sacral spinal cord in spinal cord intact and chronic spinal cord injured cats," *Experimental Neurology*, vol. 190, no. 1, pp. 171–183, 2004.

[5] C. Tai, J. Wang, X. Wang, W. C. De Groat, and J. R. Roppolo, "Bladder inhibition or voiding induced by pudendal nerve stimulation in chronic spinal cord injured cats," *Neurourology and Urodynamics*, vol. 26, no. 4, pp. 570–577, 2007.

[6] W. A. Scheepens, G. A. Van Koeveringe, R. A. De Bie, E. H. J. Weil, and P. E. V. Van Kerrebroeck, "Urodynamic results of sacral neuromodulation correlate with subjective improvement in patients with an overactive bladder," *European Urology*, vol. 43, no. 3, pp. 282–287, 2003.

[7] D. B. Vodusek, J. K. Light, and J. M. Libby, "Detrusor inhibition induced by stimulation of pudendal nerve afferents," *Neurourology and Urodynamics*, vol. 5, no. 4, pp. 381–389, 1986.

[8] R. A. Appell and T. B. Boone, "Surgical management of overactive bladder," *Current Bladder Dysfunction Reports*, vol. 2, pp. 37–45, 2007.

[9] P. Zvara, S. Sahi, and M. M. Hassouna, "An animal model for the neuromodulation of neurogenic bladder dysfunction," *British Journal of Urology*, vol. 82, no. 2, pp. 267–271, 1998.

[10] M. B. Chancellor and E. J. Chartier-Kastler, "Principles of sacral nerve stimulation (SNS) for the treatment of bladder and urethral sphincter dysfunctions," *Neuromodulation*, vol. 3, no. 1, pp. 15–26, 2000.

[11] F. Van Der Pal, J. P. F. A. Heesakkers, and B. L. H. Bemelmans, "Current opinion on the working mechanisms of neuromodulation in the treatment of lower urinary tract dysfunction," *Current Opinion in Urology*, vol. 16, no. 4, pp. 261–267, 2006.

[12] H. A. Shaw and L. J. Burrows, "Etiology and treatment of overactive bladder in women," *Southern Medical Journal*, vol. 104, no. 1, pp. 34–39, 2011.

[13] E. J. McGuire, S. C. Zhang, E. R. Horwinski, and B. Lytton, "Treatment of motor and sensory detrusor instability by electrical stimulation," *Journal of Urology*, vol. 129, no. 1, pp. 78–79, 1983.

[14] G. Amarenco, S. S. Ismael, A. Even-Schneider et al., "Urodynamic effect of acute transcutaneous posterior tibial nerve stimulation in overactive bladder," *Journal of Urology*, vol. 169, no. 6, pp. 2210–2215, 2003.

[15] W. Yoong, A. E. Ridout, M. Damodaram, and R. Dadswell, "Neuromodulative treatment with percutaneous tibial nerve stimulation for intractable detrusor instability: outcomes following a shortened 6-week protocol," *BJU International*, vol. 106, no. 11, pp. 1673–1676, 2010.

[16] S. Kabay, S. C. Kabay, M. Yucel et al., "The clinical and urodynamic results of a 3-month percutaneous posterior tibial nerve stimulation treatment in patients with multiple sclerosis-related neurogenic bladder dysfunction," *Neurourology and Urodynamics*, vol. 28, no. 8, pp. 964–968, 2009.

[17] K. M. Peters, S. A. Macdiarmid, L. S. Wooldridge et al., "Randomized trial of percutaneous tibial nerve stimulation versus extended-release tolterodine: results From the overactive bladder innovative therapy trial," *Journal of Urology*, vol. 182, no. 3, pp. 1055–1061, 2009.

[18] R. A. Schmidt, H. Bruschini, and E. A. Tanagho, "Sacral root stimulation in controlled micturition. Peripheral somatic neurotomy and stimulated voiding," *Investigative Urology*, vol. 17, no. 2, pp. 130–134, 1979.

[19] R. A. Schmidt, "Advances in genitourinary neurostimulation," *Neurosurgery*, vol. 19, no. 6, pp. 1041–1044, 1986.

[20] E. A. Tanagho and R. A. Schmidt, "Electrical stimulation in the clinical management of the neurogenic bladder," *Journal of Urology*, vol. 140, no. 6, pp. 1331–1339, 1988.

[21] M. Spinelli, G. Giardiello, A. Arduini, and U. Van den Hombergh, "New percutaneous technique of sacral nerve stimulation has high initial success rate: preliminary results," *European Urology*, vol. 43, no. 1, pp. 70–74, 2003.

[22] M. Spinelli, G. Giardiello, M. Gerber, A. Arduini, U. Van Den Hombergh, and S. Malaguti, "New sacral neuromodulation lead for percutaneous implantation using local anesthesia: description and first experience," *Journal of Urology*, vol. 170, no. 5, pp. 1905–1907, 2003.

[23] N. Kohli and D. Patterson, "InterStim therapy: a contemporary approach to overactive bladder," *Reviews in Obstetrics and Gynecology*, vol. 2, no. 1, pp. 18–27, 2009.

[24] R. A. Schmidt, E. Senn, and E. A. Tanagho, "Functional evaluation of sacral nerve root integrity. Report of a technique," *Urology*, vol. 35, no. 5, pp. 388–392, 1990.

[25] J. Pannek, U. Grigoleit, and A. Hinkel, "Bacterial contamination of test stimulation leads during percutaneous nerve stimulation," *Urology*, vol. 65, no. 6, pp. 1096–1098, 2005.

[26] K. M. Borawski, R. T. Foster, G. D. Webster, and C. L. Amundsen, "Predicting implantation with a neuromodulator using two different test stimulation techniques: a prospective randomized study in urge incontinent women," *Neurourology and Urodynamics*, vol. 26, no. 1, pp. 14–18, 2007.

[27] K. M. Peters, J. M. Carey, and D. B. Konstandt, "Sacral neuromodulation for the treatment of refractory interstitial cystitis: outcomes based on technique," *International Urogynecology Journal and Pelvic Floor Dysfunction*, vol. 14, no. 4, pp. 223–228, 2003.

[28] K. Everaert, W. Kerckhaert, H. Caluwaerts et al., "A prospective randomized trial comparing the 1-stage with the 2-stage implantation of a pulse generator in patients with pelvic floor dysfunction selected for sacral nerve stimulation," *European Urology*, vol. 45, no. 5, pp. 649–654, 2004.

[29] M. Spinelli and K. D. Sievert, "Latest technologic and surgical developments in using InterStim™ therapy for sacral neuromodulation: impact on treatment success and safety," *European Urology*, vol. 54, no. 6, pp. 1287–1296, 2008.

[30] R. A. Janknegt, E. H. J. Weil, and P. H. A. Eerdmans, "Improving neuromodulation technique for refractory voiding dysfunctions: two-stage implant," *Urology*, vol. 49, no. 3, pp. 358–362, 1997.

[31] T. M. Kessler, H. Madersbacher, and G. Kiss, "Prolonged sacral neuromodulation testing using permanent leads: a more reliable patient selection method?" *European Urology*, vol. 47, no. 5, pp. 660–665, 2005.

[32] T. M. Kessler, E. Buchser, S. Meyer et al., "Sacral neuromodulation for refractory lower urinary tract dysfunction: results of a nationwide registry in switzerland," *European Urology*, vol. 51, no. 5, pp. 1357–1363, 2007.

[33] W. A. Scheepens, E. H. J. Weil, G. A. Van Koeveringe et al., "Buttock placement of the implantable pulse generator: a new implantation technique for sacral neuromodulation—a multicenter study," *European Urology*, vol. 40, no. 4, pp. 434–438, 2001.

[34] D. Y. Deng, M. Gulati, M. Rutman, S. Raz, and L. V. Rodríguez, "Failure of sacral nerve stimulation due to migration of tined lead," *Journal of Urology*, vol. 175, no. 6, pp. 2182–2185, 2006.

[35] A. Wagg, A. Majumdar, P. Toozs-Hobson, A. K. Patel, C. R. Chapple, and S. Hill, "Current and future trends in the management of overactive bladder," *International Urogynecology Journal and Pelvic Floor Dysfunction*, vol. 18, no. 1, pp. 81–94, 2007.

[36] A. Hijaz, S. P. Vasavada, F. Daneshgari, H. Frinjari, H. Goldman, and R. Rackley, "Complications and troubleshooting of two-stage sacral neuromodulation therapy: a single-institution experience," *Urology*, vol. 68, no. 3, pp. 533–537, 2006.

[37] M. S. Elkelini and M. M. Hassouna, "Safety of MRI at 1.5 tesla in patients with implanted sacral nerve neurostimulator," *European Urology*, vol. 50, no. 2, pp. 311–316, 2006.

[38] O. J. Wiseman, U. V. D. Hombergh, E. L. Koldewijn, M. Spinelli, S. W. Siegel, and C. J. Fowler, "Sacral neuromodulation and pregnancy," *Journal of Urology*, vol. 167, no. 1, pp. 165–168, 2002.

[39] C. L. Amundsen, A. A. Romero, M. G. Jamison, and G. D. Webster, "Sacral neuromodulation for intractable urge incontinence: are there factors associated with cure?" *Urology*, vol. 66, no. 4, pp. 746–750, 2005.

[40] N. D. Sherman, M. G. Jamison, G. D. Webster, and C. L. Amundsen, "Sacral neuromodulation for the treatment of refractory urinary urge incontinence after stress incontinence surgery," *American Journal of Obstetrics and Gynecology*, vol. 193, no. 6, pp. 2083–2087, 2005.

[41] E. H. J. Weil, J. L. Ruiz-Cerdá, P. H. A. Eerdmans, R. A. Janknegt, B. L. H. Bemelmans, and P. E. V. Van Kerrebroeck, "Sacral root neuromodulation in the treatment of refractory urinary urge incontinence: a prospective randomized clinical trial," *European Urology*, vol. 37, no. 2, pp. 161–171, 2000.

[42] R. T. Foster Sr., E. J. Anoia, G. D. Webster, and C. L. Amundsen, "In patients undergoing neuromodulation for intractable urge incontinence a reduction in 24-hr pad weight after the initial test stimulation best predicts long-term patient satisfaction," *Neurourology and Urodynamics*, vol. 26, no. 2, pp. 213–217, 2007.

[43] R. K. Leong, S. G. G. De Wachter, and P. E. V. Van Kerrebroeck, "Current information on sacral neuromodulation and botulinum toxin treatment for refractory idiopathic overactive bladder syndrome: a review," *Urologia Internationalis*, vol. 84, no. 3, pp. 245–253, 2010.

[44] R. A. Schmidt, U. Jonas, K. A. Oleson et al., "Sacral nerve stimulation for treatment of refractory urinary urge incontinence. Sacral Nerve Stimulation Study Group," *Journal of Urology*, vol. 162, no. 2, pp. 352–357, 1999.

[45] M. M. Hassouna, S. W. Siegel, A. A. B. Lycklama À Nÿeholt et al., "Sacral neuromodulation in the treatment of urgency-frequency symptoms: a multicenter study on efficacy and safety," *Journal of Urology*, vol. 163, no. 6, pp. 1849–1854, 2000.

[46] S. E. Sutherland, A. Lavers, A. Carlson, C. Holtz, J. Kesha, and S. W. Siegel, "Sacral nerve stimulation for voiding dysfunction: one institution's 11-year experience," *Neurourology and Urodynamics*, vol. 26, no. 1, pp. 19–28, 2007.

[47] P. E. V. van Kerrebroeck, A. C. van Voskuilen, J. P. F. A. Heesakkers et al., "Results of sacral neuromodulation therapy for urinary voiding dysfunction: outcomes of a prospective, worldwide clinical study," *Journal of Urology*, vol. 178, no. 5, pp. 2029–2034, 2007.

[48] A. C. Van Voskuilen, D. J. A. J. Oerlemans, E. H. J. Weil, R. A. De Bie, and P. E. V. A. Van Kerrebroeck, "Long term results of neuromodulation by sacral nerve stimulation for lower urinary tract symptoms: a retrospective single center study," *European Urology*, vol. 49, no. 2, pp. 366–372, 2006.

[49] A. C. Van Voskuilen, D. J. A. J. Oerlemans, E. H. J. Weil, U. Van Den Hombergh, and P. E. V. A. Van Kerrebroeck, "Medium-term experience of sacral neuromodulation by tined lead implantation," *BJU International*, vol. 99, no. 1, pp. 107–110, 2007.

[50] F. Cappellano, P. Bertapelle, M. Spinelli et al., "Quality of life assessment in patients who undergo sacral neuromodulation implantation for urge incontinence: an additional tool for evaluating outcome," *Journal of Urology*, vol. 166, no. 6, pp. 2277–2280, 2001.

[51] E. Chartier-Kastler, P. Ballanger, M. Belas et al., "Sacral neuromodulation with InterStim™ system: results from the French national register," *Progres en Urologie*, vol. 21, pp. 209–217, 2010.

[52] R. K. Leong, T. A. Marcelissen, F. H. Nieman, R. A. De Bie, P. E. Van Kerrebroeck, and S. G. De Wachter, "Satisfaction and patient experience with sacral neuromodulation: results of a single center sample survey," *Journal of Urology*, vol. 185, no. 2, pp. 588–592, 2011.

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Clinical Study

Solifenacin in Multiple Sclerosis Patients with Overactive Bladder: A Prospective Study

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Objective. To assess the efficacy and the effect on Qol of solifenacin for the treatment of OAB in MS patients. *Patients and Methods*. Thirty MS patients suffering from OAB were treated with solifenacin 5/10 mg for 8 weeks. The first 4 weeks patients received solifenacin 5 mg. At week 4 patients could request a dose increase to 10 mg. The efficacy was evaluated at 8 weeks. *Results*. After 4 weeks of treatment, 28 patients reported acceptable or no side effects. 17 continued the study with the 10 mg dosage, and 11 stayed on 5 mg solifenacin. Two patients withdrew from the study due to side effects. Solifenacin 5/10 mg for 8 weeks resulted in a significant decrease in number of micturitions and number of pads used per day compared to baseline. Also the severity of urgency prior to voiding decreased significantly, and an increase was seen in the volume per void. Twenty out of 30 patients chose to continue solifenacin therapy after termination of the study. The majority of patients reported global QoL improvement. *Conclusions*. Solifenacin is effective in the treatment of MS patients with OAB symptoms. This is the first study with solifenacin in a specific neurogenic patient group with a neurogenic disease-specific QoL outcome measure (MS-QoL 54).

1. Introduction

Solifenacin is a once-daily oral antimuscarinic agent that has been available in The Netherlands since September 2004 for the treatment of overactive bladder (OAB). The efficacy and safety of solifenacin has already been demonstrated in randomised, double-blind placebo controlled studies [1, 2]. However, the efficacy of solifenacin in multiple sclerosis (MS) patients with symptoms of OAB is unclear, since underlying neurological disease was an exclusion criterion in previous clinical studies. The aim of the present study was to assess the efficacy of solifenacin in MS patients with symptoms of OAB. To our knowledge to date this is the first and only study in which the efficacy of solifenacin for symptoms of OAB is evaluated in a neurogenic patient population.

2. Patients and Methods

This is a prospective, open-label study to assess the efficacy and effect on quality of life of solifenacin 5/10 mg for 8 weeks in the treatment of MS patients with symptoms of OAB. The study protocol was approved by the local ethics committee of the University Medical Centre Nijmegen (CMO no. 2004/194). Patients provided written informed consent before enrolment.

Men and women with a classified MS diagnosis according to the criteria of McDonald et al. [3] and symptoms of OAB were eligible for screening and study enrolment. Inclusion and exclusion criteria are listed in Table 1. None of the patients experienced a clinical relapse of their MS within 3 months prior to inclusion. Patients were evaluated at the outpatient clinic for symptoms of OAB by history, uroflowmetry, and determination of residual urine. Most patients underwent a urodynamic workup, but this was not mandatory for inclusion in the protocol.

All medication that could influence bladder function was stopped at least 2 weeks prior to treatment or continued with no dose changes during the study. Patients were not allowed to use other antimuscarinic drugs prescribed for bladder dysfunction 2 weeks prior to or during the study. All

Table 1

Inclusion criteria (patients were eligible if all of the following applied)
(1) Classified MS diagnosis
(2) Written informed consent has been obtained
(3) Patients are willing and able to complete the micturition diary correctly
(4) Complaints of OAB
(a) Urgency/Frequency (micturition frequency > 8/day)
(b) Urge incontinence (involuntary loss of urine after a sensation of urge)
Exclusion criteria (patients would be excluded from participation if any of the following apply)
(1) Significant postvoid residual volume (PVR >200 mL)
(2) Evidence of a urinary tract infection, chronic inflammation such as interstitial cystitis, bladder stones, previous pelvic radiation therapy, or previous or current malignant disease of the pelvic organs
(3) Uncontrolled narrow angle glaucoma, urinary or gastric retention, or any other medical condition which in the opinion of the investigator makes the use of anticholinergics contra-indicated
(4) Non-drug treatment including electrostimulation therapy or start of a bladder training program during the 12 weeks prior to or during the study
(5) Use of drugs intended to treat urinary incontinence
(6) Known or suspected hypersensitivity to other anticholinergics or lactose
(7) Any clinical significant condition, which in the opinion of the investigator makes the patient unsuitable for the trial
(8) Pregnancy or the wish to become pregnant during the study

methods, units, and definitions used in this study were done according to ICS standards [4].

At baseline patients were evaluated by 72-hour voiding diaries, as well as an MS-specific quality of life questionnaire (MS-QoL 54). The MS-QoL 54 is a multidimensional health-related quality of life measure that combines both generic and MS-specific items to a single instrument [5].

In the voiding diary the voiding frequency, voided volume per void, severity (degree) of urgency prior to any void, number of incontinence periods, severity of incontinence periods, and number of pads used were recorded. The degree of urgency was described on a scale of 0–3 (i.e., 0, no urge to void; 1, moderate urge to void; 2, normal urge to void that can still be suppressed; 3, severe urge to void that cannot be suppressed). The severity of urine loss was described on a scale of 0–3 (i.e., 0, no urine loss; 1, loss of some drops; 2, loss of a small amount; 3; severe loss possibly leading to a change of clothes).

Patients that met all inclusion criteria, and none of the exclusion criteria received solifenacin 5/10 mg for 8 weeks. All patients received solifenacin 5 mg once daily in the the first 4 weeks. At week 4, patients could continue 5 mg solifenacin treatment for another 4 weeks or request a dose escalation to 10 mg once daily in case of subjective insufficient efficacy and no or acceptable side effects.

Both solifenacin 5 and 10 mg once daily have been shown to be effective and well tolerated for treating symptomatic OAB [6]. A starting dose of 5 mg solifenacin was chosen because of the somewhat favourable efficacy/side-effect ratio compared to 10 mg solifenacin.

After a total treatment period of 8 weeks the efficacy of solifenacin was evaluated by 72-hour voiding diary and MS-QoL 54. Global patient perception was assessed by enquiring patient satisfaction and the patients' desire to continue the treatment.

Primary endpoints were defined as change from baseline in mean number of micturition per 24 hours, change from baseline in mean voided volume per void, and change from baseline in number of incontinence episodes per 24 hours and number of pads used per 24 hours. Change in quality of life (QoL), as measured with the MS-QoL 54, was a secondary endpoint.

Changes from baseline to endpoint were subjected to the Wilcoxon signed-ranks test.

The quality of life questionnaires were compared using the test for paired samples correlations (paired t-test).

3. Results

Between January and July 2005, 30 patients with MS and OAB symptoms were enrolled in this clinical study. All patients (12 men and 18 women) were diagnosed with OAB. Nine patients suffered from "OAB-dry" and 21 of "OAB-wet" Seven patients had received antimuscarinic therapy in the past without the desired effect. Twenty-three patients have not been treated with antimuscarinic agents prior to inclusion in the protocol. No patients had received other therapy than oral antimuscarinics for the OAB symptoms prior to the study.

After 4 weeks of treatment with solifenacin 5 mg, 28 patients reported acceptable or no side effects. Two patients withdrew from the study due to adverse events (gastrointestinal complaints and skin rash.) Both adverse events fully disappeared within days from discontinuation of the therapy.

Of the remaining 28 patients, 11 patients (39%) chose to continue treatment with the 5 mg dosage. Seventeen (61%)

Table 2

	Baseline (IQD) $n = 30$	After 8 weeks of treatment (IQD) $n = 28$	Wilcoxon signed ranks Test
Median frequency/day	11.7 (9.3–13.4)	9.5 (6.9–10.9)	$P = .000$
Median volume voided/void	121.9 (103.1–152.9)	155.3 (103.1–198.2)	$P = .000$
Median incontinence episodes/day	1.3 (0.0–2.7)	0.2 (0.0–1.7)	$P = .360$
Median no. pads used/day	2.0 (0.0–3.4)	1.0 (0.0–2.0)	$P = .010$
Median severity of urine loss (0–3; daily added score)	1.2 (0.0–5.0)	0.3 (0.0–2.8)	$P = .053$
Median degree of urgency prior to voiding (0–3; daily added score)	36.3 (28.8–47.3)	23.7 (18.0–31.0)	$P = .000$

patients requested a dose escalation to 10 mg solifenacin due to subjective insufficient efficacy.

Evaluation of the voiding diaries after 8 weeks of treatment compared to baseline showed a significant decrease in median number of micturitions (-2.2 episodes/24 hours, $P < .0001$) and number of pads used per 24 hours ($-1{,}0$ pads/24 hours, $P = .010$). Also the degree of urgency prior to voiding decreased significantly (-12.6, $P < .0001$). Additionally a significant increase with 33 mL ($P < .0001$) was seen in the median voided volume per void. Whilst the median number of incontinence episodes per 24 hours and the median severity of urine loss improved numerically, these changes were not statistically significant (Table 2). This could be due to the low number of patients that were incontinent at study baseline.

Although many patients thus reported a subjective improvement in QoL, this was not apparent when analysing the MS-QoL 54. Only one of the subscales, health perception, showed a borderline significant increase of 0.8 points ($P = .041$). All other MS-QoL 54 subscales detected no significant differences from baseline to end of study (Table 3).

Global patient perception evaluation showed that 22 out of 30 patients (73%) chose to continue solifenacin therapy after the study, due to beneficial effects. Six patients (20%) chose to terminate the use of the drug because of lack of effect. Only in 2 out of 30 (7%) patients the reason for discontinuation of therapy was side effects.

4. Discussion

Lower urinary tract symptoms are common in MS. Up to 90% of patients have voiding complaints at some time during the course of the disease, especially with a disease duration longer than 10 years [7]. The most common voiding complaints are urgency, occurring in 24–86%, and urge incontinence, reported in 34–72% of patients [8].

Unlike the bladder dysfunction that follows spinal cord injury and causes life-threatening upper urinary tract conditions, MS very rarely causes severe upper urinary tract involvement but rather results in morbidity that influences the quality of life [9].

Anticholinergic agents are commonly used in the management of the OAB. For more than 30 years oxybutynin has been the drug of choice in patients with a neurogenic cause of OAB. Randomised controlled studies comparing oxybutynin to other antimuscarinic agents in neurogenic patients date from the late 1980s and early 1990s [10, 11]. A lot of neurogenic patients need a higher dose to achieve clinical efficacy [12]. With the introduction of tolterodine in 1999 a new antimuscarinic agent was added to the management options op OAB. Tolterodine is said to be equally effective compared to oxybutynin, but with a better side-effect profile [13]. Ethans et al. published the first randomised, controlled study comparing these two agents in neurogenic patients. It consisted of merely 10 patients [14]. In 2004 solifenacin was introduced for the treatment of OAB symptoms. In all pivotal studies neurogenic causes of an overactive bladder were considered an exclusion criterion [6, 15]. Therefore the efficacy of solifenacin in patients suffering from lower urinary tract dysfunction due to MS (or any other neurogenic cause) is unclear. However, OAB symptoms are very common in MS patients, and antimuscarinics are frequently prescribed, although the evidence for this indication is low. Therefore, even clinical studies with a relatively simple design are valuable in a specific group like MS patients.

Most of the time neurogenic patients are excluded from registration studies because they respond differently to medical treatments or they deal differently with common primary endpoints in OAB studies such as micturition frequency. When a wheelchair-bound patient has to tell you how many times he or she goes to the toilet per day, the answer will be highly dependent, amongst others, on environmental factors such as the availability of proper wheelchair toilets. Moreover MS is a progressive disease, so the clinical endpoint may differ from baseline to end of study even without intervention. The issue is that we do not have objective parameters to define a stable patient, apart from that MS patients are not a homogeneous group and that they may have all kinds of disabilities.

This study shows that solifenacin is effective in the treatment of MS patients with OAB symptoms when assessed by means of 72-hour voiding diaries. Significant improvements were observed on severity of urgency, frequency and urge incontinence and number of pads used in 24 hours. Also subjective improvements evaluated by means of the global patient perception question suggested that patients were satisfied with the efficacy of solifenacin on their

Table 3

$N = 28$		Mean	Std. deviation	Std. error mean	P value
Physical health	T1	25.9	19.7	4.8	.191
	T2	27.4	22.9	5.6	
Role limitation (physical)	T1	25.0	35.4	8.6	.173
	T2	32.4	35.1	8.5	
Role limitation (emotional)	T1	68.6	39.9	9.7	.985
	T2	62.7	42.3	10.3	
Pain	T1	68.2	28.9	7.0	.963
	T2	82.3	23.4	5.7	
Emotional well-being	T1	77.6	20.2	4.9	.761
	T2	72.7	13.2	3.2	
Energy	T1	47.5	22.5	5.5	.740
	T2	47.3	18.0	4.4	
Health perception	T1	36.2	18.2	4.4	.041
	T2	37.4	15.6	3.8	
Social function	T1	54.9	12.9	3.1	.631
	T2	58.8	12.3	3.0	
Cognitive function	T1	66.5	26.9	6.5	.669
	T2	76.5	19.0	4.6	
Health distress	T1	67.1	21.2	5.1	.517
	T2	69.4	21.4	5.2	
Sexual function	T1	44.6	31.3	7.6	.203
	T2	51.0	32.1	7.8	
Change in health	T1	27.9	26.3	6.4	.409
	T2	36.8	28.1	6.8	
Sexual satisfaction	T1	35.3	36.5	8.9	.394
	T2	44.1	37.0	9.0	
Overall QoL	T1	58.2	13.2	3.2	.725
	T2	57.7	12.0	2.9	
MS QoL54 (physical)	T1	44.3	15.3	3.7	.446
	T2	48.4	15.4	3.7	
MS QoL54 (mental)	T1	68.8	20.6	5.0	.863
	T2	67.7	17.5	4.2	
MS QoL54 (total)	T1	113.1	33.9	8.2	.955
	T2	116.1	30.9	7.5	

symptoms. 73% of patients wanted to continue therapy due to favourable results. We recognize that the study design is limited by the absence of a control group. It would be useful to do a head to head comparison in a randomized controlled trial in the future.

The effects on QoL, measured with the MS-QoL 54, were not apparent. The developers of the MS-QoL 54 utilized the Short Form 36 (SF-36) as the generic component to which 18 items were added to tap MS-specific issues [5]. It contains 54 questions distributed among 12 subscales (with 2 summary scores) and 2 single-item measures. The MS-QoL 54 contains only one question concerning bladder and/or bowel function (no. 51) and there is a subscale that specifically measures urological function/perception. Question 51 of the MS-QoL 54 informs about the degree in which patient were limited in their social activities during the last 4 weeks as result of their bladder and/or bowel dysfunction. We hypothesize that for this reason the MS-QoL 54 may be not sensitive enough to detect changes in the QoL due to lower urinary tract functioning. The domains of physical health, physical role limitations, health, perception and sexual function do show a trend towards increased QoL. Since lower urinary tract symptoms cause a substantial decrease in quality of life also in MS patients we expected that the improvement in lower urinary tract symptoms would have caused improvements in other domains of the MS-QoL 54 as well [16]. Therefore we think that the study is too small to show this effect. Urological problems are of major importance in the lives of MS patients, so we suggest that this domain should be incorporated in an MS-specific quality of life measuring instrument.

5. Conclusion

Solifenacin is efficacious in treating OAB symptoms in MS patients. Solifenacin significantly improved frequency, severity of urgency, volume voided, and number of pads used per 24 hours.

The MS-QoL 54 showed no significant changes, other than a modest improvement in one of the subscales. Possibly, MS-QoL 54 is not specific enough to detect changes in OAB symptoms in an MS patient population. Further randomised clinical studies with antimuscarinics in this specific patient group are warranted.

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References

[1] C. R. Chapple, P. Araño, J. L. H. R. Bosch, D. De Ridder, A. E. J. L. Kramer, and A. M. Ridder, "Solifenacin appears effective and well tolerated in patients with symptomatic idiopathic detrusor overactivity in a placebo- and tolterodine-controlled phase 2 dose-finding study," *British Journal of Urology International*, vol. 93, no. 1, pp. 71–77, 2004.

[2] C. R. Chapple, L. Cardozo, W. D. Steers, and F. E. Govier, "Solifenacin significantly improves all symptoms of overactive bladder syndrome," *International Journal of Clinical Practice*, vol. 60, no. 8, pp. 959–966, 2006.

[3] W. I. McDonald, A. Compston, G. Edan et al., "Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the Diagnosis of Multiple Sclerosis," *Annals of Neurology*, vol. 50, no. 1, pp. 121–127, 2001.

[4] P. Abrams, L. Cardozo, M. Fall et al., "The standardisation of terminology of lower urinary tract function: report from the standardisation sub-committee of the international continence society," *Neurourology and Urodynamics*, vol. 21, no. 2, pp. 167–178, 2002.

[5] B. G. Vickrey, R. D. Hays, R. Harooni, L. W. Myers, and G. W. Ellison, "A health-related quality of life measure for multiple sclerosis," *Quality of Life Research*, vol. 4, no. 3, pp. 187–206, 1995.

[6] C. R. Chapple, T. Rechberger, S. Al-Shukri et al., "Randomized, double-blind placebo-and tolterodine-controlled trial of the once-daily antimuscarinic agent solifenacin in patients with symptomatic overactive bladder," *British Journal of Urology International*, vol. 93, no. 3, pp. 303–310, 2004.

[7] E. J. McGuire and J. A. Savastano, "Urodynamic findings and long-term outcome management of patients with multiple sclerosis-induced lower urinary tract dysfunction," *Journal of Urology*, vol. 132, no. 4, pp. 713–715, 1984.

[8] C. D. Betts, M. T. D'Mellow, and C. J. Fowler, "Urinary symptoms and the neurological features of bladder dysfunction in multiple sclerosis," *Journal of Neurology Neurosurgery and Psychiatry*, vol. 56, no. 3, pp. 245–250, 1993.

[9] E. L. Koldewijn, O. R. Hommes, W. A. J. G. Lemmens, F. M. J. Debruyne, and P. E. V. Van Kerrebroeck, "Relationship between lower urinary tract abnormalities and disease- related parameters in multiple sclerosis," *Journal of Urology*, vol. 154, no. 1, pp. 169–173, 1995.

[10] J. B. Gajewski and S. A. Awad, "Oxybutynin versus propantheline in patients with multiple sclerosis and detrusor hyperreflexia," *Journal of Urology*, vol. 135, no. 5, pp. 966–968, 1986.

[11] J. W. Thuroff, B. Bunke, A. Ebner et al., "Randomized, double-blind, multicenter trial on treatment of frequency, urgency and incontinence related to detrusor hyperactivity: oxybutynin versus propantheline versus placebo," *Journal of Urology*, vol. 145, no. 4, pp. 813–817, 1991.

[12] N. Bennett, M. O'Leary, A. S. Patel, M. Xavier, J. R. Erickson, and M. B. Chancellor, "Can higher doses of oxybutynin improve efficacy in neurogenic bladder?" *Journal of Urology*, vol. 171, no. 2 I, pp. 749–751, 2004.

[13] S. R. Serels and R. A. Appell, "Tolterodine: a new antimuscarinic agent for the treatment of the overactive bladder," *Expert Opinion on Investigational Drugs*, vol. 8, no. 7, pp. 1073–1078, 1999.

[14] K. D. Ethans, P. W. Nance, R. J. Bard, A. R. Casey, and O. I. Schryvers, "Efficacy and safety of tolterodine in people with neurogenic detrusor overactivity," *Journal of Spinal Cord Medicine*, vol. 27, no. 3, pp. 214–218, 2004.

[15] L. Cardozo, M. Lisec, R. Millard et al., "Randomized, double-blind placebo controlled trial of the once daily antimuscarinic agent solifenacin succinate in patients with overactive bladder," *Journal of Urology*, vol. 172, no. 5 I, pp. 1919–1924, 2004.

[16] G. Quarto, R. Autorino, A. Gallo et al., "Quality of life in women with multiple sclerosis and overactive bladder syndrome," *International Urogynecology Journal and Pelvic Floor Dysfunction*, vol. 18, no. 2, pp. 189–194, 2007.