REVIEW

Neurogenic detrusor overactivity in adults: a review on efficacy, tolerability and safety of oral antimuscarinics

H Madersbacher¹, G Mürtz² and M Stöhrer³

Objectives: This review analyzed efficacy, tolerability and safety of oral antimuscarinic (AM) drugs in adults suffering from neurogenic detrusor overactivity (NDO).

Methods: A comprehensive search of major literature bases was conducted to identify all references.

Results: Thirty studies, thereof 16 randomized controlled trials (RCT), enrolling 1479 patients were identified and included in the review. Results were grouped in dose-finding, placebo- and active-controlled, flexible dose and combined high-dose AM drugs, and various studies. Key urodynamic outcome parameters, such as maximum detrusor pressure and maximum cystometric bladder capacity, demonstrated the efficacy of AM in NDO, following 2–3 weeks of treatment. Contrary to idiopathic detrusor overactivity (IDO), no placebo effects manifested. Other important parameters, such as impact on the upper urinary tract function and morphology, issues of continence, post-void residual urine, catheterisation, urinary tract infections and quality of life, were investigated to a limited extent only. Incidence rates of adverse events were comparable for NDO and IDO. Most of the studies, especially RCT, were undertaken with oxybutynin immediate release (IR), trospium chloride IR, propiverine IR and propiverine extended release. In NDO, these drugs are best investigated.

Conclusions: AM drugs are effective in NDO, they normalize the intravesical pressure and increase cystometric bladder capacity. However, other important parameters are not adequately investigated so far and should be recognized in future studies.

Spinal Cord (2013) **51**, 432–441; doi:10.1038/sc.2013.19

Keywords: antimuscarinic drugs; neurogenic detrusor overactivity; efficacy; tolerability and safety of antimuscarinics; neurogenic bladder; humans

INTRODUCTION

Recently published reviews on antimuscarinic (AM) drugs focus either on idiopathic detrusor overactivity (IDO)/overactive bladder (OAB),¹ or on bladder outlet obstruction and lower urinary tract (LUT) symptoms.^{2,3} Studies on neurogenic detrusor overactivity (NDO) were not included in these reviews, although AM alone or in combination with intermittent catheterisation (IC) are the mainstay for NDO therapy: ‘AM drugs are the first-line choice for treating neurogenic LUT (NLUTD). They are the most useful medication available for NLUTD and provide an established approach to managing NDO (level of evidence 1a).’⁴

The aim of AM treatment in NDO is different from IDO, as detrusor pressure during filling and voiding is crucial. Lowering or normalizing the detrusor pressure with AM is an important goal, demanding urodynamic work-up and follow-up. Consequently, AM ‘prevent renal and bladder damage and potentially improve long-term outcomes (LE 1a).’⁴ This is in contrast to IDO/OAB, in which improvement of the key symptoms, urgency with or without incontinence, frequency and nocturia, is intended.

In the only meta-analysis focussing on NDO, Madhuvrata *et al.*⁵ restricted their approach to 16 randomized controlled trials (RCT), however, with a rather statistical than clinical approach and inclusion

criteria deviant from our review. The review did not address issues such as bladder compliance, duration of detrusor contractions, IC, and function and morphology of the upper urinary tract.

This review aims at analyzing the efficacy, tolerability and safety of AM in adults suffering from NDO. Although only the RCTs in this review give the core information according to evidence-based criteria, all publications on this topic with respect to the criteria given below are included, thus providing comprehensive information, also unmasking deficits and unmet clinical needs, which should be addressed in future studies.

MATERIALS AND METHODS

Search strategy

The review is based on a comprehensive search of all major literature bases (MEDLINE, EMBASE) and abstract books from annual meetings of the American Association of Urology, International Continence Society, European Association of Urology and International Medical Society of Paraplegia from January 1986 to February 2012 (Figure 1: body of evidence). The following search terms were used: AM drugs, darifenacin, fesoterodine, imidafenacin, oxybutynin, propiverine, solifenacin, tolterodine, trospium chloride, propantheline, NDO, detrusor hyperreflexia, adults and human. There were no restrictions on the inclusion of publications by language. Publications in languages other than English were included, if an abstract in English was

¹Department of Neurology, Medical University Innsbruck, Innsbruck, Austria; ²Cologne, Germany and ³Department of Urology and Paediatric Urology, University of Essen, Essen, Germany

Correspondence: Professor H Madersbacher, Department of Neurology, Medical University Innsbruck, Anichstrasse 35, Innsbruck 6020, Austria.

E-mail: helmut.madersbacher@tilak.at

Received 23 August 2012; revised 13 February 2013; accepted 21 February 2013

Figure 1 Body of evidence.

Table 1a Dose-finding studies—summary of study characteristics

Author	LE	Study design	Treatment dura- tion (weeks)	Treatment groups	Patient number (N)	Gender	Age (years)	Diagnosis ^a
Mazur <i>et al.</i> ¹⁰	1b	Prospective, rando- mized, parallel group, multicentre (4)	3	1 × 15 mg Prop IR (N = 14) 2 × 15 mg Prop IR (N = 21) 3 × 15 mg Prop IR (N = 17) 4 × 15 mg Prop IR (N = 14)	66	33 male 33 female	48/40/43/43 years in the 4 treatment arms	Neurogenic reflex incontinence (post-trau- matic, postoperative, myelitis, myelodegenerative)
van Kerrebroeck <i>et al.</i> ¹¹	1b	Prospective, rando- mized, parallel group, double- blind, placebo-con- trolled, multicentre (14)	2	Placebo (N = 19) 2 × 0.5 mg Tolt IR (N = 20) 2 × 1.0 mg Tolt IR (N = 16) 2 × 2.0 mg Tolt IR (N = 18) 2 × 4.0 mg Tolt IR (N = 17)	90 enrolled, 76 per protocol	48 male 42 female	42 years	Detrusor hyperreflexia (MS 23, paraplegia 20, quadriplegia 11, spinal cord diseases 8, mis- cellaneous 21)
Stöhrer <i>et al.</i> ¹²	1b	Prospective, rando- mized, parallel group, double- blind, placebo- controlled	2	Placebo (N = 16) 2 × 10 mg TC IR (N = 16) 2 × 20 mg TC IR (N = 17) 2 × 40 mg TC IR (N = 17)	66 enrolled, 63 analyzed	NA	NA	Detrusor hyperreflexia > 6 months in most patients

Abbreviations: IR, immediate release; LE, level of evidence; MS, multiple sclerosis; NA, not applicable; Prop, propiverine; Tolt, tolterodine; TC, trosipium chloride.

^aTerminology used by the original study authors has been retained.

available. Inclusion criteria comprised patients with proven NDO and an age of ≥ 18 years. Case studies and studies enrolling 'mixed' patient populations of IDO and NDO were not included.

There were nine AM included in this review: darifenacin, fesoterodine, imidafenacin, oxybutynin, propiverine, solifenacin, tolterodine, trosipium chloride and propantheline for historic reasons. AM were administered at

Table 1b Placebo-controlled studies—summary of study characteristics

Author	LE	Study Design	Treatment duration (weeks)	Treatment groups	Patient number (N)	Gender	Age (years)	Diagnosis ^a
Stöhrer <i>et al.</i> ¹³	1b	Prospective, randomized, parallel group, double-blind, placebo-controlled, multicentre (2)	3	3 × 1 Placebo 3 × 5 mg Oxy IR	60	NA.	NA	Detrusor hyperreflexia in spinal cord injured patients and upper motor neuron lesion
Stöhrer <i>et al.</i> ¹⁵	1b	Prospective, randomized, parallel group, double-blind, placebo-controlled, multicentre (3)	3	Placebo (<i>N</i> = 32) 2 × 20 mg TC IR (<i>N</i> = 29)	61 enrolled 55 analyzed	30 male, 25 female	A. M. 32.3 (TC) 34.2 (Plac.)	Spinal cord injury with consecutive detrusor hyperreflexia
Stöhrer <i>et al.</i> ¹⁴	1b	Prospective, randomized, parallel group, prospective, double-blind, multicentre (4)	2	3 × 1 Placebo 3 × 15 mg Prop IR	113	69 male, 44 female	30 ± 11.7 (Prop.) 29.2 ± 10.9 (Plac.)	Detrusor hyperreflexia and suprasacral spinal cord injury
Ethans <i>et al.</i> ¹⁶	2b	Prospective, randomized, cross-over, double-blind, monocentre	2 weeks for each cross-over period, intermediate 4-day-wash-out period	Placebo (<i>N</i> = 10) 2 × 2 mg Tolt IR (<i>N</i> = 10)	14 enrolled 10 completed	9 male, 1 female	A. M. 40.5 (range 21–63)	NDO due to SCI (7), MS (2), spina bifida (1)
Amarenco <i>et al.</i> ¹⁷	1b	Prospective, randomized, double-blind, multicentre (NA)	4	Placebo (<i>N</i> = 40), Solifenacin 1 × 10 mg (<i>N</i> = 51)	NA	NA	18–65	NDO due to SCI (81) or MS (95)

Abbreviations: A. M., arithmetic mean; IR, immediate release; LE, level of evidence; MS, multiple sclerosis; NA not applicable; NDO, neurogenic detrusor overactivity; Oxy, oxybutynin; Prop, propiverine; SCI, spinal cord injury; Tolt, tolterodine; TC, trospium chloride.

^aTerminology used by the original study authors has been retained.

various doses, dose intervals and by various immediate (IR) and extended release (ER) formulations. Our review is restricted to orally administered AM. Intravenous,⁶ transdermal,⁷ and intravesical, alone or combined with oral⁸ formulations, are either clinically not relevant (intravenous) or data were too scarce.

Key urodynamic parameters, such as maximum detrusor pressure and maximum cystometric bladder capacity, and clinical parameters, such as the achievement of continence, the need for catheterisation, autonomic dysreflexia, and impact on upper urinary tract function and morphology, urinary tract infections (UTI) and quality of life (QoL) were reviewed. Typical AM adverse events (AE), dry mouth rates and discontinuation rates served as tolerability and safety outcome parameters.

Statistical analysis

Owing to the limited number of studies in the different categories, statistical analyses were considered as not feasible.

RESULTS

Study characteristics

The studies were grouped as dose-finding (Table 1a), placebo-controlled (Table 1b), active-controlled (Table 1c), flexible dose and combined high-dose AM (Table 1d), and various, and classified according to their LE.⁹ Studies investigating flexible and combined high-dose AM share the common characteristic that applied doses are not in conformity with doses recommended in the respective summary of product characteristics. Altogether, 30 studies, thereof 16 RCT, enrolling 1479 patients were analyzed. Study details, such as

design, treatment duration, treatment groups, patient number, gender, age and diagnosis are given in the respective tables. Most patients suffered from suprasacral spinal lesions, mostly due to spinal cord injury (SCI). In none of the RCT, a majority of patients presenting with suprapontine NDO was enrolled, and studies enrolling both clinical entities did not analyze subpopulations separately.

Dose-finding studies. Three dose-finding studies (Table 1a), two of them placebo-controlled, were conducted with propiverine IR,¹⁰ tolterodine IR¹¹ and trospium chloride IR.¹²

Placebo-controlled studies. The study characteristics of the five placebo-controlled proof of efficacy studies with oxybutynin IR,¹³ propiverine IR,¹⁴ trospium chloride IR,¹⁵ tolterodine IR¹⁶ and solifenacin¹⁷ are summarized in Table 1b.

Active-controlled studies. Six active-controlled studies (Table 1c) compared oxybutynin IR with propantheline IR,¹⁸ oxybutynin IR with trospium chloride IR,¹⁹ oxybutynin IR with propiverine IR,²⁰ oxybutynin IR with tolterodine IR,¹⁶ propiverine IR with propiverine ER²¹ and solifenacin with oxybutynin.¹⁷

Flexible dose studies and combined high-dose AM. Six studies investigated, whether flexible dosing improved therapeutic response (Table 1d), two with oxybutynin ER,^{22,23} one with trospium chloride IR,²⁴ one with solifenacin,²⁵ one compared oxybutynin IR with tolterodine IR,¹⁶ another tolterodine ER with trospium chloride

Table 1c Active-controlled studies—summary of study characteristics^a

Author	LE	Study design	Treatment Duration (weeks)	Treatment groups	Patient number (N)	Gender	Age (years)	Diagnosis ^b
Madersbacher <i>et al.</i> ¹⁹	1b	Prospective, randomized, parallel group, double-blind, multicentre (5)	2	2 × 20 mg TC IR (N = 52), 3 × 5 mg Oxy IR (N = 43)	95 enrolled, 88 analyzed	47 male, 48 female	32.8 (TC) 31.3 (Oxy)	Detrusor hyperreflexia due to SCI
Gajewski <i>et al.</i> ¹⁸	1b	Prospective, randomized, parallel group	6–8	3 × 5 mg Oxy IR (N = 19), 3 × 15 mg Propantheline IR (N = 15)	34	8 male, 26 female	NA	Multiple sclerosis with detrusor hyperreflexia
Ethans <i>et al.</i> ¹⁶	2b	Prospective, cross-over, open-label, double-blind, monocentre	2	8.4 mg/day Tolt IR, 12.5 mg/day Oxy IR (Doses self-selected by the patients)	14 enrolled, 10 completed	9 male, 1 female	40.5 (range 21–63)	NDO due to SCI (7), MS (2), spina bifida (1)
Stöhrer <i>et al.</i> ²⁰	1b	Prospective, randomized, parallel group, double-blind, multicentre (20)	3	3 × 15 mg Prop IR (N = 70), 3 × 5 mg Oxy IR (N = 61)	131 enrolled, 107 ITT, 91 PP	99 male, 32 female	38.8 (Prop) 37.7 (Oxy)	NDO: SCI (122), myelitis (1), MS (2), myelodysplasia (4), spinal tumor (2)
Stöhrer <i>et al.</i> ²¹	1b	Prospective, randomized, parallel group, double-blind, multicentre (6)	3	3 × 15 mg Prop IR, 1 × 45 mg Prop ER	66	41 male, 25 female	41.4 (Prop IR) 40.9 (Prop ER)	Neurogenic detrusor overactivity

Abbreviations: ER, extended release; IR, immediate release; ITT, intention to treat; LE, level of evidence; MS, multiple sclerosis; NA not applicable; NDO, neurogenic detrusor overactivity; Oxy, oxybutynin; PP, per protocol; Prop, propiverine; SCI, spinal cord injury; Tolt, tolterodine; TC, trospium chloride.

^aThe results of the study of Amarenco *et al.*¹⁷ comparing solifenacin and oxybutynin are not yet reported, so far only the comparison of solifenacin with placebo is reported.

^bTerminology used by the original study authors has been retained.

IR.²⁶ Two studies combined high-dose AM in patients nonresponsive to dosage-escalated monotherapy.^{27,28}

Various studies. Nine studies were grouped as various studies: one investigated short-term efficacy of trospium chloride IR,²⁹ one the onset of efficacy of tolterodine IR³⁰ and another tolterodine ER.³¹ Three studies, one with darifenacin³² and two with solifenacin were open-label, noncomparative studies.^{33,34} Three studies investigated long-term outcomes of propiverine IR,³⁵ and fesoterodine,³⁶ another open-label retrospective study compared tolterodine with oxybutynin.³⁷ The studies of Tan and Toh,³⁷ and Yamanishi *et al.*³¹ lack important study details.

Efficacy

Dose-finding studies. Based on the urodynamic results the dose-finding studies showed distinct dose–response relationships, reflected in a decrease of maximum detrusor pressure and paralleled by an increase of maximum cystometric capacity.^{10–12} These effects were superior to placebo, if a placebo arm was incorporated.^{11,12}

Placebo- and active-controlled studies. The results with respect to the key efficacy outcome parameters, maximum detrusor pressure and maximum cystometric bladder capacity, are summarized in Tables 2a and 2b: Comparing AM with placebo resulted in significant differences with negligible effects of placebo.^{13–15} Unequivocally, placebo- and active-controlled studies with reported urodynamic outcomes demonstrated a significant decrease of ~30–40% in maximum detrusor pressure, paralleled by a significant increase of maximum

cystometric bladder capacity of ~30–40% for oxybutynin IR, propiverine IR, propiverine ER and trospium chloride IR.^{13–15,19–21} The effects of solifenacin 10 mg were distinctly less pronounced.¹⁷ Moreover, equieffectivity of oxybutynin IR 5 mg t.i.d. and trospium chloride IR 20 mg b.i.d.,¹⁹ and oxybutynin IR 5 mg t.i.d. and propiverine IR 15 mg t.i.d.²⁰ was shown. Propiverine IR 15 mg t.i.d. and propiverine ER 45 mg s.i.d. proved to be equieffective in regards to the primary efficacy outcome parameter reflex volume.²¹

Results on changes of bladder compliance and in duration of detrusor contraction¹⁴ were incompletely or not at all reported. This applies also to upper urinary tract function and morphology (Tables 2a and 2b).

Flexible dose studies and combined high-dose AM. All studies with flexible doses (Table 1d) ended up with higher doses compared with those in studies with fixed doses: Self-selected dosing of oxybutynin IR, up to 15 mg per day, and tolterodine IR, up to 12 mg per day, resulted in improved efficacy without compromising tolerability.¹⁶ In a dose titration study of oxybutynin ER, 74.4% of patients requested daily doses of at least 15 mg; doses up to 30 mg were effective and well tolerated.²² Doubling the recommended AM dosage in patients nonresponsive to recommended doses improved urodynamic parameters significantly.²⁶ Moreover, the same authors showed that 85% of patients nonresponsive to dosage-escalated monotherapy could be treated successfully by combined high-dose AM.²⁷

Various studies. Geirsson *et al.*³⁰ investigated the onset of efficacy, following single doses of tolterodine IR, which manifested as early as

Table 1d Flexible dose studies and combined high-dose AM—summary of study characteristics

Author	LE	Study design	Treatment duration (weeks)	Treatment groups	Patient number (N)	Gender	Age (years)	Diagnosis ^a
<i>Flexible dose</i>								
O'Leary <i>et al.</i> ²³	2a	Prospective, open-label, dose titration, monocentre	12	Dose titration: Oxy ER 10–30 mg	10	4 male, 6 female	49.0 (range 35–77)	Complete or incomplete SCI with urodynamically defined detrusor hyperreflexia
Bennett <i>et al.</i> ²²	2a	Prospective, open-label, dose titration, monocentre	12	Dose titration: Oxy ER 10–30 mg	39	10 male, 29 female	46.3 ± 7.2	Neurogenic bladder: MS (22), SCI (10), Morbus Parkinson (7)
Ethans <i>et al.</i> ¹⁶	2b	Prospective, open-label, double-blind, monocentre	2	2 groups (doses self-selected by the patients): Oxy IR + Tolt IR	14 enrolled, 10 completed	9 male, 1 female	40.5 (Range 21–63)	NDO due to SCI (7), MS (2), spina bifida (1)
Menarini <i>et al.</i> ²⁴	1b	Prospective, double-blind, randomized, active-control, parallel groups, multicentre (10)	3–5	2 groups (TC IR): (1) standard dose: 45 mg per day (2) adjustable dose: increase up to 90 or 135 mg day dependent on urodynamic response	80 enrolled	66 male, 10 female	36 ± 11 years (adjustable dose) 36 ± 13 years (standard dose)	NDO
Persu <i>et al.</i> ²⁵	2a	Prospective, open-label, monocentre	3 months	Group 1: Solifenacin 10 mg Group 2: Dose increment to Solifenacin 20 mg after 1 month	29	19 males, 10 female	NA	SCI 10, MS 6, Morbus Parkinson 5, stroke 6
Horstmann <i>et al.</i> ²⁶	1b	Prospective, randomized, 2 parallel groups	4 weeks	2 groups: (1) Tolt ER 8 mg (2) TC IR 90 mg	21	15 male, 6 female	34 (18–55)	NDO: SCI 17, MS 3, MMC 1
<i>Combined high-dose AM</i>								
Amend <i>et al.</i> ²⁷	3	Open-label	4 weeks	3 groups: (1) Tolt 8 mg + Oxy 15–30 mg (2) TC IR 90 mg + Tolt 4–8 mg (3) Oxy 30 mg + TC IR 45–90 mg	27	21 male, 6 female	35.7	NDO: SCI 21, MS 3, MMC 1.
Cameron <i>et al.</i> ²⁸	3	Retrospective chart review	Variable treatment periods	3 groups dependent on whether prior AM therapy or not and whether on 2 or 3 AM during treatment	77	70% male, 30% female	39.3 (17.5–77.6)	SCI 49, MMC 13, other diagnoses 15

Abbreviations: ER, extended release; IR, immediate release; LE, level of evidence; MS, multiple sclerosis; NA not applicable; NDO, neurogenic detrusor overactivity; Oxy, oxybutynin; SCI, spinal cord injury; Tolt, tolterodine; TC, trospium chloride.

^aTerminology used by the original study authors has been retained.

0.5 hours post dosing. Orally administered darifenacin was effective in an uncontrolled, open-label study in patients with NDO due to multiple sclerosis (MS).³² Two uncontrolled, open-label studies with limited number of patients were undertaken with solifenacin.^{33,34} van Rey and Heesakkers³⁴ showed clinical improvements for micturition frequency, pad use and voided volume in patients with MS; no urodynamic data were given.

Clinical, long-term and QoL outcomes

Frequency and mode of bladder emptying, for example, IC, as well as autonomic dysreflexia, were not addressed in a way, allowing sound

conclusions. Moreover, only few of the placebo- and active-controlled studies investigated achievement of continence in detail^{20,21} or to a limited extent.^{16,18} Stöhrer *et al.*²⁰ reported a decrease of 1.3 incontinence episodes following oxybutynin IR compared with a decrease of 1.6 episodes following propiverine IR; however, details on adjunct IC are not given. Effects of AM on UTI, upper urinary tract function and morphology are not reported.

Long-term efficacy of AM was demonstrated in three studies: Propiverine IR showed constant efficacy during a 1-year follow-up, the efficacy profile favored 45 mg compared with 30 mg.³⁵ In a study with SCI patients comparing tolterodine and oxybutynin tolterodine

Table 2a Placebo-controlled studies—efficacy outcomes^a

		Stöhrer et al. ^{13b}		Stöhrer et al. ¹⁵		Stöhrer et al. ¹⁴		Ethans et al. ¹⁶	
		Oxy IR 3 × 5 mg	Placebo	TC IR 2 × 20 mg	Placebo	Prop IR 3 × 15 mg	Placebo	Tolt IR 2 × 2 mg	Placebo
N		60 overall		29	32	60	53	14 overall	
Urodynamic parameters									
Max. cystometric bladder capacity (ml)	Pre	175	240	171	185	262	296	NA	NA
	Post	<u>300</u>	<u>230</u>	<u>309</u>	<u>NA</u>	<u>366</u>	<u>289</u>	<u>322</u>	<u>244</u>
	Post-pre	+ 125	− 10	+ 138	− 17	+ 104	− 7	NA	NA
	P _{intra}	0.0001	0.80	NA	NA	0.0001	NA	NA	NA
	P _{inter}	p _{Oxy-Plac} : <0.0001		p _{TC-Plac} : <0.001		NA		NA	
Max. detrusor pressure (cm H ₂ O)	Pre	90	85	101	82	81	92	NA	NA
	Post	<u>55</u>	<u>81</u>	<u>NA</u>	<u>NA</u>	<u>54</u>	<u>92</u>	NA	NA
	Post-pre	− 35	− 4	− 38	− 2	− 27	0	NA	NA
	P _{intra}	0.0001	0.013			0.001	NA		NA
	P _{inter}	p _{Oxy-Plac} : <0.0001		p _{TC-Plac} : <0.001		p _{Prop-Plac} : 0.0001		NA	
PVR (ml)	Pre	17	13	34	20	50	59	NA	NA
	Post	<u>32</u>	<u>16</u>	<u>NA</u>	<u>NA</u>	<u>87</u>	<u>61</u>	NA	NA
	Post-pre	+ 15	+ 3	+ 15	+ 15	+ 37	+ 2	NA	NA
	P _{intra}	0.0001	0.37	NA	NA	NA	NA	NA	NA
	P _{inter}	p _{Oxy-Plac} : 0.012		p _{TC-Plac} :0.80		p _{Prop-Plac} : 0.01		NA	
Clinical parameters									
Incontinence	Pre	NA	NA	NA	NA	NA	NA	1(0.1–3.5) ^c	2.8(0–3.6) ^c
	Post	NA	NA	NA	NA	NA	NA	NA	NA
	Post-pre	NA	NA	NA	NA	NA	NA	NA	NA
Upper urinary tract		NA	NA	NA	NA	NA	NA	NA	NA
QoL		NA	NA	NA	NA	NA	NA	NA	NA

Abbreviations: IR, immediate release; NA not applicable; Oxy, oxybutynin; *P*_{intra}, within group comparisons (post vs. pre values); *P*_{inter}, inter-group comparisons (comparison of the post vs. pre values of both groups); Prop, propiverine; PVR, post-void residual urine; Tolt, tolterodine; TC, trospium chloride.

^aThe study of Amarenco *et al.*¹⁷ is not included in this table, because detailed results are not given.

^bValues of the urodynamic parameters according to figures provided by authors.

^cTolterodine significantly superior to placebo in reduction of incontinence episodes.

demonstrated an increasing cystometric bladder capacity over a mean follow-up period of 3 years, whereas oxybutynin did not (no dosages given).³⁷ Fesoterodine 4 mg showed significant improvements of micturition frequency and incontinence episodes in MS patients after a mean follow-up period of 22 months.³⁶

QoL was investigated in three open-label studies: Some domains of the King's Health Questionnaire were significantly improved following tolterodine.³¹ With solifenacin, a disease-specific QoL outcome measure showed only modest improvements in one of the subscales, investigating patients with MS.³⁴ With 4 mg fesoterodine, a global improvement in QoL was observed in patients with MS already after 1 month, and was maintained during follow-up of 22 months.³⁶

Tolerability and safety

All studies (Tables 3a and 3b), exempting one,¹⁵ showed either lower overall AE or dry mouth rates, or discontinuation rates for placebo compared with AM.^{13,14,16,17} The most frequently reported AE was dry mouth, higher incidence rates are reported for oxybutynin IR compared with trospium chloride IR,¹⁹ tolterodine¹⁶ and propiverine.²⁰ Higher doses of AM were not necessarily associated

with higher rates of AE.^{22,24,27} The combination of two different AM, administered in higher-than-recommended dosages, revealed increased rates of AE, resulting in a drop-out rate of 15% because of typical AM AE. The three long-term studies^{35–37} reported AE rates of up to 13%,³⁵ and drop-out rates of 27%, due to side effects or unsatisfactory outcomes.³⁶

DISCUSSION

The aim of treatment in NDO is to preserve upper urinary tract function and to manage incontinence, possibly to restore continence, by achieving a low detrusor pressure with adequate bladder capacity and regular bladder emptying, with tolerable or without post-void residual (PVR).⁴ In contrast to IDO/OAB, AM drugs decrease the maximum detrusor pressure in NDO³⁸ up to ~40 cm H₂O, as was shown in SCI patients.^{13–15,19–21} According to Mc Guire's *et al.*³⁹ findings, this is the crucial detrusor leak point pressure in children with NLUTD due to myelomeningocele. However, there is no evidence for this threshold value in adults. The magnitude of pressure reduction is correlated with its baseline value. This may be the reason why in the study of Amarenco *et al.*¹⁷ with a mixed patient

Table 2b Active-controlled studies—efficacy outcomes

Gajewski and Awad ¹⁸				Madersbacher et al. ¹⁹				Stöhrer et al. ²⁰				Stöhrer et al. ²¹				Ethans et al. ¹⁶																							
Oxy IR 3 × 5 mg				Propantheline IR 3 × 15 mg				Oxy IR 3 × 5 mg				Prop IR 3 × 15 mg				Prop ER 1 × 45 mg				Oxy IR 12.5 mg per day				Tolt IR 8.4 mg per day															
N				19				15				43				52				45				46				33				33				14 overall			
Urodynamic parameters																																							
Max. cysto-metric bladder capacity (ml)				Pre	138	163		188	215	164	198	124	107	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA									
				Post	282	198		351	312	298	309	229	204	562	454																								
				Post-pre	+144	+35		+166	+97	+134	+110	+104	+98	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA								
				P _{intra}	NA	NA		0.001	0.001	S	S	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA								
				P _{inter}	NA	NA		0.001	0.001	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS								
PTC-Oxy: 0.06																																							
Max. detrusor pressure (cm H ₂ O)				Pre	NA	NA		82	82	69	57	66	67	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA									
				Post	NA	NA		44	53	43	38	42	44	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA								
				Post-pre	NA	NA		-38	-29	-26	-19	-24	-23	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA								
				P _{intra}	NA	NA		0.001	0.001	S	S	0.0043	<0.0001	<0.0001	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA							
				P _{inter}	NA	NA		0.001	0.001	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS							
PTC-Oxy: 0.63																																							
PVR (ml)				Pre	NA	NA		48	49	65	73	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA										
				Post	NA	NA		154	128	149	141	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA								
				Post-pre	NA	NA		+106	+79	+84	+68	+18	+17	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA								
				P _{intra}	NA	NA		0.001	0.001	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA							
				P _{inter}	NA	NA		0.001	0.001	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS							
PTC-Oxy: 0.18																																							
Clinical parameters																																							
Incontinence				Pre	NA	NA		NA	NA	3.3	3.9	79.3%	80.6%	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA										
				Post	NA	NA		NA	NA	2.0	2.3	65.5%	41.9%	0.5	0.6																								
				Post-pre	-1.0	-0.5		NA	NA	-1.3	-1.6	-13.8%	-38.7%	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA								
				P _{intra}	NA	NA		NA	NA	<0.05	<0.05	NS	0.0005	Both groups were comparable (NS) in reduction of incontinence episodes/day																									
				P _{inter}	NA	NA		NA	NA	p _{Prop-Oxy} : 0.54	p _{PropIR-PropER} : 0.041																												
p _{PropIR-PropER} : 0.0005																																							
Upper urinary tract				Pre	NA	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA										
				Post	NA	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA								
p _{PropIR-PropER} : 0.041																																							
QoL				Pre	NA	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA										
				Post	NA	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA								

Abbreviations: ER, extended release; IR, immediate release; NA, not applicable; NS, not significant; Oxy, oxybutynin; P_{intra}, within group comparisons (post vs. pre values); P_{inter}, inter-group comparisons (comparison of the post vs. pre values of both groups); Prop, propiverine; PVR, post-void residual urine; S, significant; Tolt, tolterodine; TC, trospium chloride.

Abbreviations: ER, extended release; IR, immediate release; NA, not applicable; NS, not significant; Oxy, oxybutynin; P_{intra}, within group comparisons (post vs. pre values); P_{inter}, inter-group comparisons (comparison of the post vs. pre values of both groups); Prop, propiverine; PVR, post-void residual urine; S, significant; Tolt, tolterodine; TC, trospium chloride.

Table 3a Placebo-controlled studies—tolerability and safety outcomes^a

	<i>Stöhrer et al.</i> ¹³		<i>Stöhrer et al.</i> ¹⁵		<i>Stöhrer et al.</i> ¹⁴		<i>Ethans et al.</i> ¹⁶	
	<i>Oxy IR 3 × 5 mg</i>	<i>Placebo</i>	<i>TC IR 2 × 20 mg</i>	<i>Placebo</i>	<i>Prop IR 3 × 15 mg</i>	<i>Placebo</i>	<i>Tolt IR 2 × 2 mg</i>	<i>Placebo</i>
AE	70%	13%	1/ 29 (3%)	7/ 32 (22%)	NA	NA	NA	NA
Dry mouth	> 50%	NA	NA	NA	22/ 60 (37%)	4/ 53 (8%)	1.7 (0–6.7) Visual analog scale	0.7 (0–2.4) Visual analog scale
Methodology of assessing AE	NA		Spontaneously reported		Actively prompted		NA	
Discontinuations	2	3	2/ 29 (7%)	4/ 32 (13%)	8/ 60 (13%)	3/ 53 (5.6%)	NA	NA

Abbreviations: AE, adverse events; IR, immediate release; NA, not applicable; Oxy, oxybutynin; Prop, propiverine; Tolt, tolterodine; TC, trospium chloride.

^aThe study of Amarenco *et al.*¹⁷ comparing solifenacin and placebo is not included in this table, because detailed results are not given.**Table 3b Active-controlled studies—tolerability and safety outcomes^a**

	<i>Gajewski and Awad</i> ¹⁸		<i>Madersbacher et al.</i> ¹⁹		<i>Stöhrer et al.</i> ²⁰		<i>Stöhrer et al.</i> ²¹		<i>Ethans et al.</i> ¹⁶	
	<i>Oxy IR 3 × 5 mg</i>	<i>Propantheline IR 3 × 15 mg</i>	<i>Oxy IR 3 × 5 mg</i>	<i>TC IR 2 × 20 mg</i>	<i>Oxy IR 3 × 5 mg</i>	<i>Prop IR 3 × 15 mg</i>	<i>Prop IR 3 × 15 mg</i>	<i>Prop ER 1 × 45 mg</i>	<i>Oxy IR 12.5 mg per day</i>	<i>Tolt IR 8.4 mg per day</i>
AE	13/19 (68%)	8/15 (53%)	Almost comparable in both groups		48/61 (78.7%)	48/70 (68.6%)	48.5%	36.4%	NA	NA
Dry mouth	NA	NA	22 (56%), in 23% severe	26 (54%), in 4% severe	41/61 (67.2%)	33/70 (47.1%)	24.2%	27.3%	4.4 (0.3–6.6)	2.6 (0–8.8)
Methodology of assessing AE	NA		Actively prompted		Actively prompted		Spontaneously reported		NA	
Discontinuations	4/19 (22%)	4/15 (27%)	7 (16%)	3 (6%)	9/61 (15%)	16/70 (23%)	NA	NA	NA	NA

Abbreviations: AE, adverse events; ER, extended release; IR, immediate release; NA, not applicable; Oxy, oxybutynin; Prop, propiverine; Tolt, tolterodine; TC, trospium chloride.

^aThe study of Amarenco *et al.*¹⁷ comparing solifenacin and oxybutynin is not included in this table, because detailed results are not given.

population of MS ($N=95$) and SCI ($N=81$), the decrease in detrusor pressure at leak was only 11.7 cm H₂O.

Achieving a low intravesical pressure situation, associated with an increase in maximum cystometric bladder capacity, should improve incontinence, especially when combined with IC. However, the achievement of continence was reported in the RCTs not at all,^{13–15} only to a limited extent^{7,16,18} or rarely in detail.^{20,21} Nevertheless, for patients on IC the mere reduction of incontinence episodes is not sufficient, they want to become continent in-between catheterisations without using condom catheters or pads. This issue should be addressed in more detail in future studies. However, it has to be considered that this outcome parameter is secondary to maximum detrusor pressure, the most crucial surrogate parameter, reflecting a successful or insufficient protection of the renal function.

In contrast to IDO/OAB, PVR urine increased in most studies significantly, and thus contributed positively to the clinical situation in patients on IC, because the increase of PVR reflects detrusor relaxation, thus enhancing the chance to become continent in-between catheterisations. The reasons for the increase of PVR are two-fold: A decrease of detrusor pressure and ongoing detrusor-sphincter-dyssynergia. None of the studies defined the type and the severity of detrusor-sphincter-dyssynergia.

Most patients with NDO require long-term or even life-long AM medication. However, study duration was limited to 2–3 weeks in most studies, long-term outcomes were only scarcely addressed. Therefore, the impact of lowering the detrusor pressure on the upper urinary tract could not be investigated.^{35–37} No information is given, whether an initially normal upper urinary tract remained stable or a pathological upper urinary tract recovered. Nevertheless, the proven normalization of pressure situation following short-term treatment presents a surrogate parameter, thus most probably indicative of normalization of the upper urinary tract as long-term outcome.

The results of dose-finding and flexible dose studies confirmed that the detrusor pressure is further decreased with higher dosages. Also self-selected dosing has shown that patients preferred higher doses than recommended. This is in accordance with the Guidelines of the European Association of Urology on NLUTD, stating that ‘neurogenic patients usually need a higher dose of AM agents than patients with IDO (LE 1b).’⁴

In regards to tolerability and safety, the study results demonstrate that oxybutynin IR has the highest dry mouth rate compared with all other AM (Tables 3a and 3b), which is in accordance with the results given in the meta-analyses by Chapple *et al.*¹ and Kessler *et al.*⁴⁰ in patients with IDO/OAB. Although many neurogenic

patients may take AM life-long, only one of the studies⁴¹ addressed central nervous side effects explicitly, which are relevant also in this group of patients. Therefore, further studies, especially long-term studies, should incorporate this issue. This is especially important, because in the future more elderly, already cognitively impaired patients with NDO need AM treatment.

The fact that in flexible dose studies, AM despite higher doses, often two- or three-fold of the recommended doses, do not necessarily induce a higher overall rate of AE or dry mouth, is remarkable; a possible explanation could be the younger age of these predominantly SCI patients. The fact that the combination of two or even three AM in high doses showed an increased drop-out rate is possibly because of the fact that patients are unlikely to accept two or three drugs for the same disease at the same time.

Power considerations of study planning were not given or not taken into account. Also the statistical analysis is limited because of the small number of patients in multiple categories. Moreover, only six head-to-head-studies of the different AM drugs are available. Whether these issues may limit the validity of the conclusions is debatable. However, one has to bear in mind, that the relatively rare incidence rate of NDO compared with IDO/OAB precludes studies with comparable patient numbers. Moreover, the nonexistence of placebo effects in NDO studies may counteract the limited patient numbers.^{13–15}

The evaluation of the studies revealed some deficits, as clinically important parameters were either not evaluated or not reported: the impact of AM on bladder compliance, which was either not assessed or the results given were difficult to interpret due to nonuniform methodology;⁴² the issue, whether AM shorten a prolonged detrusor contraction, the need for IC, exact data on the achievement of continence, for example, in-between IC, the impact of AM on UTI frequency and on QoL. This deficiency with respect to QoL may be because of the fact that many studies were conducted at a time when this issue was not yet a primary research focus. The obvious drawbacks with respect to clinical, long-term and QoL parameters should be considered in future studies. Nevertheless, AM still remain the first-line treatment for NDO, even in the era of botulinum neurotoxin type A. Moreover, the impact of different underlying disorders, the impact of bladder management strategies—AM may be dosed differently in patients voiding spontaneously compared with those performing IC—cannot be assessed due to missing data.

CONCLUSIONS

AM are effective in NDO with an acceptable tolerability profile. The placebo- and active-controlled RCTs as core studies document a decrease of maximum detrusor pressure, and an increase of maximum cystometric bladder capacity. This is endorsed by uncontrolled, open-label studies. Flexible dose studies indicate that higher doses than recommended may improve the efficacy. Oxybutynin, propiverine and trospium chloride were investigated extensively, whereas darifenacin, fesoterodine, solifenacin and tolterodine were investigated only to a limited extent. Our conclusions have to be restricted primarily to patients with spinal cord lesions, as patients with suprapontine detrusor overactivity (Morbus Parkinson, stroke, dementia and MS) are only included in two uncontrolled studies with limited patient numbers.

Drawbacks are the short duration in most of the studies, not allowing to document effects on upper urinary tract function and morphology. Moreover, important urodynamic findings (bladder compliance) as well as important clinical aspects were not evaluated

or not adequately reported to allow conclusions. This should be taken into account in future study planning.

DATA ARCHIVING

There were no data to deposit.

CONFLICT OF INTEREST

Helmut Madersbacher is a member of the advisory board of Allergan/Switzerland, Apogepha/Germany, Astellas/Austria, and a scientific advisor of Pohl-Boskamp/Germany. He received lecture honoraria from Allergan/Switzerland, Apogepha/Germany, Astellas/Austria, Dr Pfleger/Germany and Rottapharm-Madaus/Germany. Gerd Mürtz is a scientific advisor of Apogepha/Germany. Manfred Stöhrer received lecture honoraria from Allergan/Germany and Apogepha/Germany. He is a scientific advisor of Farco/Germany.

ACKNOWLEDGEMENTS

We are grateful to Guus Kramer and Saladin Alloussi for valuable contributions to the manuscript, and to Florian Schirm, Datamap Freiburg, Germany, for advice given with respect to statistical issues.

- Chapple C, Khullar V, Gabriel Z, Muston D, Bitoun CE, Weinstein D. The effects of antimuscarinic treatments in overactive bladder: An update of a systematic review and meta-analysis. *Eur Urol* 2008; **54**, 543–562.
- Novara G, Galfano A, Ficarra V, Artibani W. Anticholinergic drugs in patients with bladder outlet obstruction and lower urinary tract symptoms: a systematic review. *Eur Urol* 2006; **50**, 675–683.
- Kaplan SA, Roehrborn CG, Abrams P, Chapple CR, Bavendam T, Guan Z. Antimuscarinics for treatment of storage lower urinary tract symptoms in men: a systematic review. *Int J Clin Pract* 2011; **65**, 487–507.
- Stöhrer M, Blok B, Castro-Diaz D, Chartier-Kastler E, Del Popolo G, Kramer G *et al*. EAU guidelines on neurogenic lower urinary tract dysfunction. *Eur Urol* 2009; **56**, 81–88.
- Madhuvrata P, Hasafa Z, Singh M, Abdel-Fattah M. Anticholinergic drugs for adult neurogenic detrusor overactivity: a systematic review and meta-analysis. *Eur Urol* 2012; **62**, 816–830.
- Bycroft J, Leaker B, Wood S, Knight S, Shah G, Craggs M. The effect of darifenacin on neurogenic detrusor overactivity in patients with spinal cord injury. Annual meeting of the International Continence Society, Florence, Italy, 2003 *NeuroUrol Urodyn* 2003; **22**, A190.
- Kennelly MJ, Lemack GE, Foote JE, Trop CS. Efficacy and safety of oxybutynin transdermal system in spinal cord injury patients with neurogenic detrusor overactivity and incontinence: an open-label, dose-titration study. *Urology* 2009; **74**, 741–745.
- Pannek J, Sommerfeld HJ, Bötzel U, Senge T. Combined intravesical and oral oxybutynin chloride in adult patients with spinal cord injury. *Urology* 2000; **55**, 358–362.
- Oxford Centre for Evidence-based Medicine Levels of evidence (May 2011). Produced by Bob Phillips, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawessince November 1998.
- Mazur D, Göcking K, Wehnert J, Schubert G, Herfurth G, Alken RG. Clinical and urodynamic effects of oral propiverine therapy in neurogenic urinary incontinence: a multicentre dose-optimizing study. *Urology* 1994; **33**, 447–452.
- Van Kerrebroeck P, Amarenco G, Thüroff J, Madersbacher HG, Lock MT, Messelink EJ *et al*. Dose-ranging study of tolterodine in patients with detrusor hyperreflexia. *NeuroUrol Urodyn* 1998; **17**, 499–512.
- Stöhrer M, Bersch U, Göcking K, Schurch B, Kramer G. Dose finding study for treatment of detrusor hyperreflexia by trospium chloride. Presented at: Annual Meeting of the International Medical Society of Paraplegia. Iguassu, Brazil 1998.
- Stöhrer M, Frohneberg D, Loehner-Ernst D, Sauter P, Mandaika B. Oxybutynin in the treatment of detrusor hyperreflexia in patients with spinal cord injury: A multicentre randomised double-blind study. Presented at: Annual Meeting of the American Spinal Cord Injury Association. Orlando, USA 1990.
- Stöhrer M, Madersbacher H, Richter R, Wehnert J, Dreikorn K. Efficacy and safety of propiverine in SCI-patients suffering from detrusor hyperreflexia—a double-blind, placebo-controlled clinical trial. *Spinal Cord* 1999; **37**, 196–200.
- Stöhrer M, Bauer P, Giannetti BM *et al*. Effect of trospium chloride on urodynamic parameters in patients with detrusor hyperreflexia due to spinal cord injuries. A multicentre placebo-controlled double-blind trial. *Urol Int* 1991; **47**, 138–143.
- Ethans KD, Nance PW, Bard RJ, Casey AR, Schryvers OI. Efficacy and safety of tolterodine in people with neurogenic detrusor overactivity. *J Spinal Cord Med* 2004; **27**, 214–218.
- Amarenco G, Sutory M, Fagertun H, Wright M, Compion G, DeRidder D. Solifenacin is effective and well tolerated in patients with neurogenic detrusor overactivity. Preliminary results from the SONIC urodynamic study. *Eur Urol Suppl* 2012; **11**, e467.

- 18 Gajewski JB, Awad SA. Oxybutynin versus propantheline in patients with multiple sclerosis and detrusor hyperreflexia. *J Urol* 1986; **135**, 966–968.
- 19 Madersbacher H, Stöhrer M, Richter R, Burgdörfer H, Hachen HJ, Mürtz G. Trospium chloride versus oxybutynin: a randomized, double-blind, multicentre trial in the treatment of detrusor hyperreflexia. *Brit J Urol* 1995; **75**, 452–456.
- 20 Stöhrer M, Mürtz G, Kramer G, Schnabel F, Arnold EP, Wyndaele JJ. Propiverine Study Group. Propiverine compared to oxybutynin in neurogenic detrusor overactivity—results of a randomized, double blind, multicenter clinical study. *Eur Urol* 2007; **51**, 235–242.
- 21 Stöhrer M, Mürtz G, Kramer G, Warnack W, Primus G, Jinga V et al. Efficacy and tolerability of propiverine hydrochloride extended release compared to immediate release in patients with neurogenic detrusor overactivity. *Spinal Cord* 2013; **51**, 209–213.
- 22 Bennett N, O'Leary M, Patel AS, Xavier M, Erickson JR, Chancellor MB. Can higher doses of oxybutynin improve efficacy in neurogenic bladder? *J Urol* 2004; **171**, 749–751.
- 23 O'Leary M, Erickson JR, Smith CP, McDermott C, Horton J, Chancellor MB. Effect of controlled-release oxybutynin on neurogenic bladder function in spinal cord injury. *J Spinal Cord Med* 2003; **26**, 159–162.
- 24 Menarini M, Del Popolo G, Benedetto D, Haselmann J, Bödeker RH, Schwantes U et al. Trospium chloride in patients with neurogenic detrusor overactivity: Is dose titration of benefit to the patients? *Int J Clin Pharmacol Ther* 2006; **44**, 623–632.
- 25 Persu C, Gaevlete PA. Double dose of solifenacin for the treatment of neurogenic detrusor overactivity. *Eur Urol Suppl* 2012; **11**, e469.
- 26 Horstmann M, Schaefer T, Aguilar Y, Stenzl A, Sievert KD. Neurogenic bladder treatment by doubling the recommended antimuscarinic dosage. *Neurol Urodyn* 2006; **25**, 441–445.
- 27 Amend B, Hennenlotter J, Schaefer T, Horstmann M, Stenzl A, Sievert KD. Effective treatment of neurogenic detrusor dysfunction by combined high-dosed antimuscarinics without increased side-effects. *Eur Urol* 2008; **53**, 1021–1028.
- 28 Cameron AP, Clemens JQ, Latini JM, McGuire EJ. Combination drug therapy improves compliance of the neurogenic bladder. *J Urol* 2009; **182**, 1062–1067.
- 29 Madersbacher M, Stöhrer M, Richter R, Giannetti BM, Mürtz G. High-dose administration of trospium chloride in the treatment of detrusor hyperreflexia. *Urology* 1991; **30**, 260–263.
- 30 Geirsson G, Schoefield D, Haugie S, Steihdottir S, Hardardottir A, Glue P et al. Assessment of time to onset: the effect of single oral dose of tolterodine on neurogenic detrusor overactivity in spinal cord injury patients. Presented at: Annual Meeting of the International Continence Society 2006, (Abstract 309).
- 31 Yamanishi T, Mizuro T, Yoshida K, Uchiyama T, Sakakibara R. Efficacy of tolterodine ER for the treatment of neurogenic detrusor overactivity or low compliance bladder—assessment by urodynamic study. Presented at: Annual Meeting of the International Continence Society 2009, (Abstract 330).
- 32 Carl S, Laschke S. Darifenacin is also effective in neurogenic bladder dysfunction (multiple sclerosis). *Urology* 2006; **68** (Suppl), 250.
- 33 Spinelli M, Citari M, Zanollo L et al. Solifenacin in neurogenic overactive bladder. *Eur Urol Suppl* 2007; **6**, 273.
- 34 van Rey F, Heesakkers J. Solifenacin in multiple sclerosis patients with overactive bladder: a prospective study. *Adv Urol* 2011; **2011**, 834753.
- 35 Mazur D, Göcking K, Wehnert J, Dorschner W, Schubert G, Herfurth G et al. Verträglichkeit und Wirksamkeit einer Langzeittherapie mit Propiverinhydrochlorid bei neurogener Harninkontinenz. Eine multizentrische Studie. *Kontinenz* 1994; **2**, 74–78.
- 36 Proietti S, Lepri E, Lepri L, Lolli C, Gubbiotti M, Giannantonio A. Efficacy and tolerability of fesoterodine fumarate in the treatment of overactive bladder symptoms in patients affected by multiple sclerosis: Long term follow up. *Eur Urol Suppl* 2012; **11**, e468.
- 37 Tan YK, Toh KL. Tolterodine improves the compliance and cystometric capacity of adult neurogenic bladders secondary to spinal cord injury. Presented at: Annual Meeting of the International Continence Society 2009, (Abstract 331).
- 38 Digesu GA, Khullar V, Cardozo L, Salvatore S. Overactive bladder symptoms: do we need urodynamics? *Neurol Urodyn* 2003; **22**, 105–108.
- 39 McGuire EJ, Woodside JR, Borden TA, Weiss RM. Prognostic value of urodynamic testing in myelodysplastic patients. *J Urol* 1981; **126**, 205–209.
- 40 Kessler TM, Bachmann LM, Minder C, Löhner D, Umbehre M, Schünemann HJ et al. Adverse event assessment of antimuscarinics for treating overactive bladder: A network meta-analytic approach. *PLoS One* 2011; **6**, e16718.
- 41 Uchiyama T, Sakakibara R, Liu Z et al. The effects of anticholinergic drugs on cognitive impairment, mental dysfunction and motor dysfunction in patients with neurological disease. *35th Annual Meeting of the ICS, 28 August-2 September 2005 Montreal, Canada*. Conference Proceedings.
- 42 Wyndaele JJ, Gammie A, Bruschini H, De Wachter S, Fry CH, Jabr RI et al. Bladder compliance what does it represent: Can we measure it, and is it clinically relevant? *Neurol Urodyn* 2011; **30**, 714–722.

Supplementary Information accompanies this paper on the Spinal Cord website (<http://www.nature.com/sc>)