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ADIS DRUG EVALUATION

Propiverine

A Review of its Use in the Treatment of Adults and Children with Overactive Bladder Associated with Idiopathic or Neurogenic Detrusor Overactivity, and in Men with Lower Urinary Tract Symptoms

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Abstract Propiverine is a well established antimuscarinic agent with a mixed mode of action in the treatment of symptoms associated with overactive bladder (OAB). As well as blocking muscarinic receptors in the detrusor muscle, the drug also inhibits cellular calcium influx, thereby diminishing muscle spasm. In patients with symptoms of OAB resulting from idiopathic detrusor overactivity (IDO) or neurogenic detrusor overactivity (NDO), propiverine demonstrated dose-dependent efficacy and tolerability, with adverse events consistent with those associated with all antimuscarinic agents. In adults with IDO, propiverine demonstrated similar efficacy to that of other antimuscarinic agents (including solifenacin, tolterodine, oxybutynin and imidafenacin) and, in adults with NDO, propiverine and oxybutynin demonstrated similar efficacy. Propiverine was generally well tolerated in these patient populations, with a lower incidence of dry mouth than that associated with oxybutynin. In men with lower urinary tract symptoms (LUTS), and in whom the presence of benign prostatic enlargement (BPE) was implicated, propiverine administered as add-on therapy to an α_1-adrenoceptor antagonist demonstrated similar or superior efficacy to that achieved with an α_1-adrenoceptor antagonist alone, and combination therapy was particularly effective in patients with urinary storage symptoms. Combination therapy was generally well tolerated, but was associated with a higher incidence of adverse events than an α_1-adrenoceptor antagonist alone. In children and adolescents with IDO/OAB or NDO, propiverine was generally more effective and better tolerated than oxybutynin. In conclusion, propiverine provides a valuable option for the treatment of adults and children with OAB associated with IDO or NDO, and in men with storage LUTS.

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1 Introduction

Overactive bladder (OAB) refers to a complex of urinary symptoms defined by the International Continence Society (ICS) as urgency, with or without urgency incontinence, usually accompanied by frequency and nocturia and without proven infection or other obvious pathology [1]. The symptom complex is suggestive of detrusor overactivity, which can be further defined as being of unknown cause (idiopathic detrusor overactivity [IDO]) or due to a neurological condition (neurogenic detrusor overactivity [NDO]) [1]. Men with OAB and lower urinary tract symptoms (LUTS) experience urinary storage symptoms (urgency, frequency and urgency incontinence), which are also suggestive of detrusor overactivity that may or may not be due to benign prostatic enlargement (BPE) [2, 3].

International estimates suggest that the prevalence of IDO/OAB is 10–17 % in adults, with incidence increasing with age [4–6]. In children, limited data suggest a somewhat similar prevalence ($\approx$17 % in Korean children aged 5–13 years [7]) to that reported in adults, but unlike in adults, prevalence decreases with age [7, 8]. The prevalence of NDO is less well defined, but all patients with central or peripheral neurological disorders are at a high risk of developing urinary tract dysfunction including detrusor overactivity [9]. BPE is common in aging men,

although estimates of prevalence vary depending on the method of assessment. In the USA, it was reported that the condition affects about 70 % of men aged 60–69 years and 80 % of men aged ≥70 years [10]. In all patients with symptoms of OAB, irrespective of the underlying cause, the impact on health-related quality-of-life (HR-QOL) can be substantial [5, 9].

Antimuscarinic agents are the standard, first-line pharmacological treatment used in patients with OAB and detrusor overactivity [11, 12]. These agents suppress involuntary smooth muscle contractions in the bladder by blocking muscarinic acetylcholine receptors. Propiverine hydrochloride (henceforth referred to as propiverine) is an antimuscarinic drug that has both anticholinergic and calcium channel blocking properties [13]. The drug has been available in immediate-release (IR) and extended-release (ER) formulations (see Section 6) in several countries for many years for the treatment of OAB and NDO. This article focuses on the efficacy of oral propiverine in adults and children with IDO/OAB or NDO, as well as when used as add-on therapy with an α_1-adrenoceptor antagonist (henceforth referred to as α_1-blocker) in men with LUTS.

Data selection

Sources: Medical literature (including published and unpublished data) on propiverine was identified by searching databases (including MEDLINE and EMBASE) for articles published since 1996, bibliographies from published literature, clinical trial registries/databases and websites (including those of regional regulatory agencies and the manufacturer). Additional information (including contributory unpublished data) was also requested from the company developing the drug.

Search strategy: MEDLINE and EMBASE search terms were 'propiverine', 'overactive bladder' and 'detrusor overactivity'. Searches were last updated 23 November 2012.

Selection: Studies in patients with overactive bladder who received propiverine. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: propiverine, benign prostatic obstruction, idiopathic or neurogenic detrusor overactivity, lower urinary tract symptoms, overactive bladder, pharmacodynamics, pharmacokinetics, therapeutic use, tolerability

2 Pharmacodynamic Properties

Propiverine is a benzilic acid derivative that has musculotropic and neurotropic effects [13]. In urinary bladder smooth muscle, propiverine blocks muscarinic receptors resulting in reduced bladder contractility, as well as inhibiting calcium influx and modulating intracellular calcium, thereby diminishing muscle spasm [13].

After oral administration, propiverine is extensively biotransformed into several active metabolites, including N-oxides M-5 and M-6, and M-14 [14, 15]. Each of the main metabolites are associated with differing pharmacodynamic properties, which contribute to the overall efficacy of the drug [14–16].

Propiverine and its major metabolites have a generally similar affinity for all muscarinic receptors (M_1–M_5), although each compound exhibited a lower affinity for the M_2 receptor than the other subtypes; the M_3 receptor subtype is the most important subtype responsible for detrusor contraction [15]. Propiverine has also been shown to have a lower affinity for cardiac M_2 receptors than some other muscarinic antagonists [13].

Propiverine and the metabolite M-5, but not M-6, were shown to bind with marked affinity to the L-type calcium channel receptors in the rat bladder [17]. In human detrusor, M-6 had a greater potency for reducing muscarinic receptor-mediated contractions than propiverine or M-5 [14]. Both isomers (*cis* and *trans*) of M-5 and M-6 inhibited electric field stimulation and carbachol- as well as KCl-induced contractions of murine and porcine detrusor smooth muscle, as well as affecting calcium influx [18].

Based on a series of studies in juvenile and adult porcine detrusor tissue, it is expected that antimuscarinic compounds, including propiverine, will induce similar responses in adults and children [19].

Recent evidence has shown that propiverine also has α_1-blockade effects [20]. In human prostate and porcine trigone, propiverine and M-14, but not M-5 and M-6, relaxed phenylephrine-induced α_1-adrenoceptor-mediated contractions in a concentration-dependent manner [20].

In addition to its antimuscarinic action, propiverine may also suppress bladder overactivity by reversing adenosine triphosphate (ATP)-induced overactivity [21]. In rats, bladder overactivity induced by intravesical ATP was suppressed by propiverine and oxybutynin (but not by atropine) [21].

In studies in the rat and dog, propiverine caused a significant increase in maximum bladder volume, and also inhibited electrically-induced periodic contractions of detrusor muscle in the dog [13]. In the mini-pig, propiverine reduced maximum bladder pressure as effectively as tolterodine, and the two drugs had generally similar effects

on mouth dryness, decreasing electrically-stimulated salivation by about 61 and 56 %, respectively [22].

Propiverine at varying concentrations was shown to concomitantly affect several cardiac ion channels, but because of respective compensatory effects, the net result on action potential duration did not increase cardiovascular risk [23]. Furthermore, in placebo-controlled, crossover studies in healthy middle-aged women and in men with coronary heart disease, no negative effects on cardiac function, including corrected QT (QTc) prolongation, QTc dispersion and T-wave shape during rest and exercise, were associated with single or multiple doses of propiverine (30 mg single dose, 15 mg three times daily for 4 days, final dose of 30 mg) [24].

3 Pharmacokinetic Properties

The pharmacokinetics of propiverine following intravenous and oral administration have been reviewed previously [25, 26]. This section focuses on pharmacokinetic data following oral administration of propiverine IR and ER determined in healthy volunteers [26, 27], supplemented with the manufacturer's prescribing information [28, 29].

After oral administration, propiverine is rapidly and almost completely absorbed from the gastrointestinal tract [25, 28]. After repeated oral doses of propiverine IR 15 mg three times daily, steady-state was achieved in 4–5 days [28]. The extent of plasma protein binding was 90–95 % for propiverine and about 60 % for the main metabolite M-5 [28]. The drug is widely distributed and undergoes intensive biotransformation by N-oxidation, side-chain hydroxylation and dealkylation to produce several active metabolites that have varying contributions to the overall clinical effect of the drug (Section 2) [25, 27].

The bioequivalence of propiverine ER to propiverine IR has been established [29]. Compared with propiverine IR, propiverine ER had a delayed absorption and a more smooth concentration-time profile, thereby enabling once-daily administration [26, 27].

Propiverine IR and ER demonstrated a dose-proportional increase in area under the concentration-time curve (AUC), and bioavailability and elimination were not influenced by the dose in randomized, crossover single- [27] and multiple-dose (Table 1) [26] studies.

After 7 days' treatment with propiverine IR 15 mg three times daily or propiverine ER 45 mg once daily, the propiverine AUC from time 0 to 24 h (AUC_{24}) was not significantly different between the two formulations (1,910 vs. 2,110 ng · h/mL) (Table 1) [26]. However, the M-5 AUC_{24} for propiverine IR three times daily was significantly ($p < 0.05$) higher than for propiverine ER once daily (11,600 vs. 10,500 ng · h/mL). At steady-state, the bioavailability of propiverine IR was not significantly different to that of propiverine ER (Table 1) [26].

Table 1 Pharmacokinetic properties of propiverine (PRO) and its major metabolite M-5 in adults. Steady-state mean values after oral administration of propiverine immediate release three times daily or extended release once daily in 24 healthy volunteers in a double-blind, double-dummy, crossover study [26]

Parameter	PRO IR 15 mg			PRO ER 45 mg
	0–8 h	8–16 h	16–24 h	0–24 h
PRO				
AUC (ng · h/mL)	698	644	568*	2,110
PTF (%)	63.8	57.4	71.9	82.0*
F (%)	60.5			57.4
$t_{½}$ (h)			15.5	22.8†
CL (mL/min)	427	518	730*	460
M-5				
AUC (ng · h/mL)	4,400	3,890	3,350*	10,500
$t_{½}$ (h)			14.0	15.9†

AUC area under the plasma concentration-time curve, *CL* clearance, *ER* extended release; *F* bioavailability, *IR* immediate release, *PTF* peak-trough fluctuations, $t_{½}$ elimination half-life

* $p < 0.05$ vs. PRO IR 0–8 h and 8–16 h, † $p < 0.05$ vs. PRO IR 16–24 h

Food intake increases the bioavailability of propiverine IR by a mean of about 1.3-fold [28]. In contrast, food intake does not affect the bioavailability of propiverine ER because the drug is not absorbed until it reaches the small intestine where absorption and efflux transport is lower than in proximal areas of the gastrointestinal tract where propiverine IR is absorbed [30]. Thus, the higher bioavailability of propiverine ER compared with propiverine IR in fasting conditions was almost negated when the drugs were taken with a fat-rich meal [30]. A recent study in healthy Chinese volunteers found no significant differences in the pharmacokinetic parameters of propiverine ER 30-mg capsules determined in fasting and non-fasting conditions [31].

In the multiple-dose study [26], the pharmacokinetics of propiverine IR were circadian time-dependent, with propiverine and M-5 AUC values being significantly ($p < 0.05$) lower following the evening dose compared with the morning dose (Table 1).

After 7 days' treatment with propiverine IR 15 mg three times daily or propiverine ER 45 mg once daily, the elimination half-lives of propiverine and M-5 were significantly longer with propiverine ER than with propiverine IR (Table 1) [26]. Following oral administration of radiolabelled propiverine ER 30 mg to healthy volunteers, 60 % of radioactivity was recovered in urine and 21 % in faeces [29]. After an oral dose, <1 % of unchanged drug is excreted in the urine.

Propiverine acts as a weak inhibitor of cytochrome P450 (CYP) 3A4, and drug interactions are possible with other drugs metabolized by this pathway [28]. However, as the effects of propiverine are small compared with classical enzyme inhibitors such as ketoconazole or grapefruit juice, a marked increase in drug concentrations of concomitantly administered agents metabolized by CYP3A4 is not expected [28]. In a study in healthy volunteers, 7 days' treatment with twice-daily propiverine 15 mg reduced hepatic and intestinal CYP3A4 activity by 0.89-fold and 0.80-fold, respectively, and the combined effect resulted in a 1.46-fold increase in the AUC of oral midazolam (2 mg) [32]. No relevant effect on CYP2C9, CYP2C19 or CYP1A2 was observed with chronic propiverine treatment [32]. The metabolism of propiverine is also mediated by flavin-monooxygenases, and dosage adjustment may be required when propiverine is coadministered with potent flavin-containing mono-oxygenase inhibitor drugs, such as methimazole [28].

The pharmacokinetics of propiverine were not altered significantly in patients with severe renal impairment (creatinine clearance <30 mL/min) or in patients with mild to moderate hepatic impairment resulting from fatty liver disease [28]. No data are available on the use of propiverine in patients with severe hepatic impairment. The pharmacokinetics of propiverine were not altered in elderly patients (aged 60–85 years) compared with younger healthy adults [28].

In children aged 5–10 years with symptoms of OAB, the disposition of repeated administration of propiverine IR was dose-related for doses <0.45 mg/kg twice daily (Table 2) [33]. Propiverine was rapidly absorbed, reaching peak plasma concentration (C_{max}) within 2 h in all dosage groups (Table 2). At steady state, AUC and C_{max} values for propiverine and M-5 were about 50–100 % higher than after a single dose [33].

Table 2 Pharmacokinetic properties of propiverine and its major metabolite M-5 in children. Steady-state mean values after oral administration of propiverine immediate release in 25 children aged 5–10 years with symptoms of overactive bladder in a dose-escalating study [33]

Parameter	PRO dose (mg/kg bid)		
	≤0.3 (mean 0.21)	0.3 to ≤0.45 (mean 0.38)	>0.45 (mean 0.64)
PRO			
AUC_3 (ng · h/mL)	144	327	316
AUC_8 (ng · h/mL)	323	701	644
C_{max} (ng/mL)	68.4	152	142
t_{max} (h)	1.63	1.5	1.25
$t_{½}$ (h)	12.2	14.5	
M-5			
AUC_3 (ng · h/mL)	1,060	2,270	2,920
AUC_8 (ng · h/mL)	2,650	5,360	6,340
C_{max} (ng/mL)	535	1,060	1,270
t_{max} (h)	1.88	1.5	1.5
$t_{½}$ (h)	10.4	9.8	

AUCx area under the plasma concentration-time curve from 0 to x h, *bid* twice daily, C_{max} peak plasma concentration, *PRO* propiverine, $t_{½}$ elimination half-life, t_{max} time to reach C_{max}

4 Therapeutic Efficacy

The efficacy of oral propiverine was compared with placebo and/or active comparators in several well designed studies in adults (Section 4.1) and children (Section 4.2) with IDO/OAB or NDO, and was also evaluated as add-on therapy to an α_1-blocker in men with LUTS (Section 4.1.3). Each section focuses on randomized, phase III studies, supplemented with data from retrospective or observational analyses; the primary source of data regarding children and adolescents with NDO is a prospective, long-term analysis of clinical evidence [34].

The propiverine dosages in clinical trials include those used most commonly in Europe (propiverine IR tablets 15 mg two or three times daily or ER capsules 30 or 45 mg once daily), and that used most commonly in Japan and Korea (propiverine IR film-coated tablets 20 mg once daily). A lower dosage (propiverine IR 10 mg tablets) was administered as add-on therapy to an α_1-blocker in some studies in men with LUTS. In this review, the propiverine dosage is reported as stated in published studies, which do not always specify the type of formulation (i.e. IR or ER). In Europe, the recommended initial dosage of 30 mg/day was based on results from a dose-finding study in patients with urgency and urgency incontinence [35].

4.1 Adults

4.1.1 In Patients with Idiopathic Detrusor Overactivity (IDO)/Overactive Bladder (OAB)

Randomized, double-blind, multicentre, phase III studies in adults with IDO/OAB included patients with a clinical diagnosis of OAB based on symptoms [36–42] and those with a clinical diagnosis based on OAB symptom assessment together with urodynamic assessment of detrusor overactivity [43–45], with corresponding outcome measures (Table 3). All studies were conducted over 2–12 weeks and, where stated, included patients with a history of ≥7–10 micturitions in 24 h, and ≥1–2 episodes of urgency or urgency incontinence in 24 h [36, 37, 39–41, 44, 45], or 3 [38] or 7 days [43] (Table 3).

All randomized studies included a run-in, screening period, and patients were required to complete a bladder diary [36–45]. Primary efficacy endpoints for each study are listed in Table 3.

Table 3 Selected baseline characteristics, inclusion and exclusion criteria in fully published, key clinical trials evaluating propiverine in adults with idiopathic detrusor overactivity/overactive bladder

Reference	Mean age (≈year)	Female (%)	Key inclusion criteria	Selected exclusion criteria	Primary endpoint
Trials evaluating clinical outcomes					
Dorschner et al. [37]	67	78	Aged ≥60 years; ≥8 voids/24 h; ≥1 incontinence episode/24 h; voided volume <300 mL/void	Acute UTI; bladder emptying disorders; PVR >20 % of voided volume	Not stated
Gotoh et al. [36]	57	76	Aged ≥20 years; OAB symptoms ≥12 weeks; ≥8 voids/24 h; ≥1 UI episode/24 h or ≥1 urgency episode/24 h	Stress incontinence; polyuria >3000 mL/24 h; PVR ≥100 mL	Voids/24 h
Homma et al. [40]	58	86	Aged ≥20 years; ≥8 voids/24 h; ≥5 incontinence episodes/week; ≥1 urgency episodes/24 h	Stress incontinence; acute UTI; PVR ≥100 mL	Incontinence episodes/ week
Jünemann et al. [38]	56	89	Aged ≥18 years; ≥2 incontinence episodes in 3 days; ≥10 voids/24 h	Stress incontinence; acute UTI; PVR ≥100 mL	Incontinence episodes/ 24 h
Lee et al. [39]	52	74	Aged ≥18 years; OAB symptoms ≥12 weeks; ≥10 voids/24 h; ≥2 urgency episodes/24 h	Stress incontinence; acute UTI	Urgency episodes/ 24 h
Yamaguchi et al. [41]	60	84	Aged ≥20 years; OAB symptoms ≥6 months; ≥8 voids/24 h; ≥3 urgency and/or UI episodes/3 days	Stress incontinence; acute UTI; PVR ≥100 mL	Voids/24 h
Trials evaluating clinical and urodynamic outcomes					
Abrams et al. [43]	52 (median)	77	Aged ≥18 years; idiopathic OAB with confirmed detrusor overactivity; ≥7 voids/24 h, ≥1 UI episodes/ 7 days and/or ≥2 urgency episodes/7 days	Stress incontinence; BOO >40 (Abrams-Griffiths no.)	Urodynamic trace from AUM
Jünemann et al. [44]	56	83	Aged ≥18 years; ≥1 unstable detrusor contraction ≥10 cmH_2O and ≥8 voids/24 h; ≥1 UI episode/24 h	Stress incontinence; acute UTI; MCC 300 mL; PVR ≥50 mL	MCC
Madersbacher et al. [45]	49	93	Aged ≥18 years; MCC ≤300 mL	Acute UTI; PVR >15 % of MCC	MCC

AUM ambulatory urodynamic monitoring, *BOO* bladder outlet obstruction, *MCC* maximum cystometric bladder capacity, *OAB* overactive bladder, *PVR* post-void residual urine, *UI* urgency incontinence, *UTI* urinary tract infection

One randomized study [36] and two non-randomized studies [46, 47] evaluated efficacy using the overactive bladder symptom score (OABSS), which is a validated, self-administered questionnaire regarding daytime frequency, night-time frequency, urgency and urgency incontinence (lower scores are indicative of less severe/troublesome symptoms) [48]. HR-QOL was assessed using the King's Health Questionnaire (KHQ) [36, 38, 40, 41, 44], an instrument specific for urinary incontinence. Ambulatory urodynamic monitoring (AUM) was used to evaluate efficacy in a 2-week, crossover study [43].

The majority of patients in all studies were female, and the median age ranged from 50 to 60 years, except for the study by Dorschner et al. [37], which was limited to elderly patients (Table 3).

Comparisons with Placebo and Noncomparative Studies: Overall, propiverine (at dosages of 20–45 mg/day for periods of 4–12 weeks) was significantly more effective than placebo in improving symptoms of OAB, including the primary endpoints of reducing the mean number of voids in 24 h [36], the mean number of urgency episodes in 24 h [39], and the mean number of incontinence episodes in 24 h [38] in randomized, double-blind studies in adults [36, 38, 39] and elderly patients [37] (Table 4).

As well as the superior efficacy demonstrated with propiverine ER and IR compared with placebo in the trial by Jünemann et al. [38] (Table 4), the non-inferiority of propiverine ER 30 mg once daily to propiverine IR 15 mg twice daily was also established ($p < 0.0001$). There were no significant differences between the two propiverine formulations for any endpoint, and results in the intent-to-treat population were similar to those observed in the per-protocol population (Table 4).

In placebo-controlled studies, increases from baseline (141–186 mL) in the mean volume of urine voided at each void ranged from 25 to 55 mL across all studies [36–41], and the difference versus placebo (−8 to 29 mL) was significant ($p < 0.05$) in all comparisons except for propiverine ER in the study by Jünemann et al., in which the placebo effect was marked (40 vs. 29 mL, respectively) [38]. The mean number of nocturia episodes was reduced during treatment with propiverine 20 mg once daily and

Table 4 Efficacy of propiverine compared with placebo in patients with idiopathic detrusor overactivity/overactive bladder. All studies were randomized, double-blind and multicentre in design. Analyses were performed in the full analysis set using the last observation carried forward [36], per-protocol population [38], intent-to-treat population [49] or evaluable patients [37, 39]

Study (duration)	Treatment	No. of pts	Mean change from BL in the no. of or episodes/24 h period					
			Voids		Urgency		UI	
			BL	EP	BL	EP	BL	EP
Adults (aged ≥18 years)								
Gotoh et al. [36]	PRO 20 mg od	284	11.0	−1.86***[a]	4.3	−2.84***	1.6	−1.18***
(12 weeks)	PL	270	11.1	−1.36[a]	4.2	−1.99	1.2	−0.68
Jünemann et al. [38]	PRO IR 15 mg bid	360	12.8	−3.69***	6.1	−2.03	3.3	−2.21***[a]
(32 days)	PRO ER 30 mg od	363	12.7	−3.63***	6.4	−2.58**	3.4	−2.47***[a]
	PL	187	13.4	−3.07	6.1	−1.61	3.5	−1.78[a]
Lee et al. [39]	PRO 20 mg od	142	12.8	−3.56**	7.4	−46 %**[a b]		
(12 weeks)	PL	79	13.0	−2.58	7.6	−31 %[a b]		
Elderly pts (aged ≥60 years)								
Dorschner et al. [37]	PRO 15 mg tid	49	8.7	−2.1**			0.9	−0.6*
(4 weeks)	PL	49	7.1	−0.6			0.4	−0.1
Children (aged 5–10 years)								
Marschall-Kehrel et al. [49]	PRO 20–30 mg/day[c]	84	8.9	−2.00***[a]			0.8	−0.50***
(8 weeks)	PL	80	9.1	−1.20[a]			1.1	−0.20

Where specified [39], evaluable pts included all randomized pts who had at least one on-treatment visit and who were >75 % compliant with study medication

bid twice daily, *BL* baseline, *EP* endpoint, *od* once daily, *pts* patients, *PL* placebo, *PRO* propiverine, *tid* three times daily, *UI* urgency incontinence

* $p < 0.05$, ** $p \leq 0.01$, ***≤ 0.001 vs. PL

[a] Primary endpoint

[b] Percentage change

[c] Dosage adjusted for body weight: 17.0–27.9 kg PRO 10 mg bid and 28.0–45.0 kg PRO 15 mg bid

placebo where reported (−0.29 vs. –0.25 [36] and −0.52 vs. –0.42 [39]), but the difference did not reach significance in either of these studies.

In all studies, patient-assessed symptoms and HR-QOL improved significantly ($p < 0.05$) more with propiverine than with placebo [36–41]. For example, in the study by Gotoh et al. [36], the mean change from baseline at week 12 in the OABSS was −3.7 with propiverine 20 mg once daily versus −2.4 with placebo ($p < 0.001$), and 7 (incontinence impact, role limitations, physical limitations, social limitations, emotions, sleep/energy and severity) of 12 domains in the KHQ score improved from baseline significantly ($p < 0.05$) more in the propiverine group than in the placebo group [36]. In the study comparing propiverine IR 15 mg twice daily and ER 30 mg once daily with placebo, similar improvements in the KHQ were reported in the propiverine groups, with respective score changes from baseline at day 32 of 19.1 and 19.2 versus 13.7 ($p < 0.05$ for both) [38]. In the study by Lee et al. [39], the urgency severity score was improved at week 12 from baseline by 41 % in the propiverine 20 mg once daily group compared with 25 % in the placebo group ($p = 0.001$), and 81 versus 66 % ($p = 0.01$) of patients in the respective groups perceived treatment benefits. Elderly patients rated their improvement in urgency ($p = 0.0015$) and incontinence ($p = 0.003$) as significantly greater with propiverine 15 mg three times daily than with placebo, with similar results reported by physicians [37].

Results of large observational studies ($n = 5565$ [50] and $n = 4390$ [51]) in clinical practice in Germany support those achieved in clinical trials. For example, in adults with urgency, urgency incontinence, or urgency and stress (mixed) incontinence who were treated with propiverine ER for 12 weeks, the mean number of incontinence episodes in 24 h decreased from 4.2 at baseline to 1.3 at week 12 (change from baseline −2.9), the mean number of voids in 24 h decreased from 13.3 to 7.9 (change from baseline −5.5), and the mean volume voided at each void increased by 69 mL (levels of significance not reported) [50]. Investigators and patients reported similar overall assessments, with 92 % rating efficacy as 'good' or 'very good' [50].

Comparisons with Other Anticholinergic Therapies: Overall, in studies comparing anticholinergic therapies, the efficacy of propiverine (20–45 mg/day for periods of 4–12 weeks) was not significantly different to that of standard dosages of imidafenacin [40], solifenacin [41], oxybutynin [45] or tolterodine [42, 44] (Table 5). However, significant differences between active treatment groups were demonstrated with some endpoints, including a greater increase from baseline in the volume of urine voided at each void with propiverine 20 mg once daily than imidafenacin 0.1 mg twice daily [40], a greater decrease in the number of voids and incontinence episodes with propiverine ER 30 mg than tolterodine ER 4 mg [42], and a greater reduction in urgency episodes with solifenacin 10 mg once daily than propiverine 20 mg once daily [41] (Table 5). In placebo-controlled studies [40, 41, 45], active treatments were more effective than placebo for most endpoints (Table 5). One exception was the reduction in episodes of nocturia (this endpoint was evaluated only in the study by Yamaguchi et al.) [41], which were reduced significantly ($p < 0.025$) more than placebo with solifenacin 10 mg once daily but not with solifenacin 5 mg or propiverine 20 mg once daily [41].

In the study by Homma et al. [40], imidafenacin 0.1 mg twice daily was shown to be non-inferior ($p = 0.0014$) to propiverine 20 mg once daily based on the primary endpoint of incontinence episodes per week, which were significantly reduced from baseline by 73.08 % with propiverine, 68.54 % with imidafenacin and 52.31 % with placebo ($p < 0.0001$ for both vs. placebo) in the per-protocol population ($n = 709$) after 12 weeks of treatment; incontinence episodes per week at baseline were 17.9, 18.6 and 17.8, respectively.

The non-inferiority of propiverine ER 30 mg once daily versus tolterodine ER 4 mg once daily was demonstrated with regard to the primary endpoint of the number of voids per 24 h in the Chinese study by Leng et al. (reported in an abstract) [42]. Indeed, propiverine was shown to be more effective than tolterodine for this endpoint in this study (Table 5) [42]. However, in a study evaluating urodynamic measures, the non-inferiority of propiverine 15 mg twice daily versus tolterodine 2 mg twice daily was not demonstrated [44]. In the per-protocol population ($n = 155$), the maximum cystometric capacity increased by 56 mL (209 mL at baseline) with propiverine versus 70 mL (203 mL at baseline) with tolterodine ($p < 0.01$ vs. baseline for both treatments) after 4 weeks of treatment [44]. Corresponding increases in the volume at first desire to void were 51 versus 56 mL ($p < 0.01$ vs. baseline for both) [44].

Improvements in the mean maximum cystometric bladder capacity from baseline were not significantly different between groups receiving propiverine 15 mg three times daily (89 mL increase from a baseline mean of 222 mL) or oxybutynin 5 mg twice daily (96 mL increase from a baseline mean of 226 mL), but both active treatments were significantly more effective than placebo (52 mL increase from a baseline mean of 211 mL) ($p = 0.0105$ and 0.0023, respectively) [45]. Corresponding improvements in the mean volume at the first desire to void were 67, 71 and 27 mL (respective baseline values were 93, 89 and 93 mL) ($p < 0.05$ vs. placebo for both), and increases in PVR were 2.9, 0.8 and 0.2 mL, respectively [45].

Ambulatory urodynamic monitoring was used to compare propiverine with oxybutynin in a randomized, double-blind, multicentre, crossover study in patients ($n = 77$) with OAB due to detrusor overactivity [43]. Patients received two of four possible treatments for 2 weeks each, with a 2-week wash-out between. Recordings were made over 4 h, including 1 h before and 3 h after the morning dose of drug. In all treatment groups (propiverine 20 mg once daily, propiverine 15 mg three times daily, oxybutynin 5 mg three times daily and placebo), the normalized scores for the total number and duration of involuntary detrusor contractions were reduced from baseline (levels of significance not reported) after 2 weeks' treatment; at baseline the normalized scores for involuntary detrusor contractions ranged from 11.5 to 15.0 and the duration of contractions ranged from 590 to 800 s (data taken from a figure) [43]. In a comparison of active treatments, oxybutynin 5 mg three times daily was associated with fewer involuntary detrusor contractions (mean difference [adjusted for baseline] of −3.8 contractions) and shorter duration of contractions (mean adjusted difference of −244 s) than propiverine 20 mg once daily ($p \leq 0.01$ for both) [43]. The difference between oxybutynin and propiverine 15 mg three times daily, and between the two propiverine dosage groups did not reach significance [43].

In randomized studies evaluating HR-QOL using the KHQ, active treatments demonstrated generally similar improvements from baseline [40, 41, 44], which were greater than placebo [40, 41]. However, compared with imidafenacin 0.1 mg twice daily, propiverine 20 mg once daily was associated with significantly greater improvement in the KHQ domains of role limitations ($p < 0.016$), emotions ($p < 0.005$) and symptom severity ($p < 0.01$) [40]. In the study by Yamaguchi et al. [41], solifenacin 10 mg was associated with greater improvement in the severity domain than propiverine 20 mg ($p < 0.05$).

In a non-randomized, crossover study in Japanese women ($n = 83$; mean age of ≈75 years) with OAB, total and individual scores of the OABSS were significantly ($p < 0.01$) improved from baseline after 8 weeks' treatment with propiverine 20 mg once daily or solifenacin 5 mg once daily [46]. Symptoms of urgency were improved further following a switch from propiverine to

Table 5 The efficacy of propiverine compared with other antimuscarinic agents in adult patients with overactive bladder. All studies were randomized, double-blind and multicentre in design and, where stated, analyses were performed in the intent-to-treat [44, 45] or full analysis set [40, 41] populations

Study (duration)	Treatment	No. of pts	Mean change from BL in the no. of or episodes/24 h period unless stated otherwise								VV/void (mL)	
			Voids		Urgency		UI		Incontinence			
			BL	EP	BL	EP	BL	EP	BL	EP	BL	EP
Homma et al. [40]	PRO 20 mg od	305	11.2	−1.80***	4.8	−2.79***	15.7[a]	−11.25[a]	18.0[a]	−12.64[a]	150	+36.07***††
(12 weeks)	IMI 0.1 mg bid	318	11.2	−1.52*	4.9	−2.35***	16.6[a]	−10.72[a]	18.6[a]	−11.67[a]	147	+19.35**
	PL	143	11.5	−1.08	5.4	−1.94	15.5[a]	−7.85[a]	17.6[a]	−8.67[a]	154	+ 9.28
Jünemann et al. [44][b]	PRO 15 mg bid	100		−2.75		−3.26				−1.20	155	+31.76
(4 weeks)	TOL 2 mg bid	101		−3.07		−3.04				−0.91	148	+28.43
Leng et al. [42][c]	PRO ER 30 mg od	162	15.2	−4.58††[d]					1.3	−0.93†	99	+41.33
(8 weeks)	TOL ER 4 mg od	162	14.7	−3.77[d]					0.6	−0.34	106	+41.25
Madersbacher et al. [45]	PRO 15 mg tid	126	10.4	−1.9	9.5	−3.1						
(4 weeks)	OXY 5 mg bid	121	12.6	−2.4	12.4	−3.0						
	PL	63	11.5	−1.0	11.3	−1.2						
Yamaguchi et al. [41]	PRO 20 mg od	384	11.4	−1.87***[d]	4.1	−2.30***	1.8	−1.19*	2.2	−1.25*	151	+36.62***
(12 weeks)	SOL 5 mg od	383	11.4	−1.93***[d]	4.4	−2.41***	2.0	−1.45***	2.4	−1.59***	153	+35.78***
	SOL 10 mg od	371	11.2	−2.19***[d]	4.5	−2.78***‡	1.9	−1.52***	2.2	−1.60***	154	+43.59***
	PL	395	11.3	−0.94[d]	4.0	−1.28	1.7	−0.69	2.0	−0.72	153	+11.67

bid twice daily, *BL* baseline, *EP* endpoint, *ER* extended release, *IMI* imidafenacin, *od* once daily, *PL* placebo, *OXY* oxybutynin, *PRO* propiverine, *pts* patients, *SOL* solifenacin, *tid* three times daily, *TOL* tolterodine, *UI* urgency incontinence, *VV* volume voided

* $p < 0.05$, ** $p < 0.01$, *** $p \leq 0.001$ vs. PL; † $p < 0.05$, †† $p \leq 0.005$ vs. active comparator; ‡ $p < 0.025$ vs. PRO

[a] Values are per week

[b] Trial designed to primarily evaluate urodynamic outcomes (results discussed in main text)

[c] Results reported in an abstract

[d] Primary endpoint

solifenacin ($p < 0.01$), but not following the switch from solifenacin to propiverine [46].

Another non-randomized analysis in Japan demonstrated significant improvements from baseline in the OABSS in patients treated with propiverine after responding poorly to previous anticholinergic treatment [47]. Patients (median age of 71 years) desiring further improvement in their OAB symptoms after receiving standard dosages of solifenacin, tolterodine or imidafenacin for periods of 4 to >12 weeks were switched to propiverine 20 mg once daily for 12 weeks. After 4 and 12 weeks of propiverine treatment, the OABSS improved significantly ($p < 0.01$ for all) from baseline, irrespective of prior therapy, among 52 patients who completed treatment as per the protocol [47].

4.1.2 *In Patients with Neurogenic Detrusor Overactivity (NDO)*

Randomized, double-blind, multicentre, phase III studies in adults (aged ≥18 years) with NDO include two 2-week studies comparing propiverine with placebo in patients with suprasacral spinal cord injuries [52] or neurological disorders [53], a 3-week, non-inferiority study comparing propiverine ER 45 mg once daily with propiverine IR 15 mg three times daily (reported in an abstract) [54], and a 3-week study comparing propiverine with oxybutynin in patients with known neurological disorders and demonstrable detrusor overactivity at urodynamic assessment [55]. Infravesical obstructions and acute urinary tract infections were among exclusion criteria [52, 53, 55].

Compared with placebo, propiverine 20 mg once daily (Japanese study) [53] or 15 mg three times daily (European study) [52] for 2 weeks was significantly more effective with regard to urodynamic parameters and clinical symptoms (Table 6). According to patient assessment of clinical symptoms in the European study, an improvement was reported in 63.3 % of propiverine recipients compared with 22.6 % of placebo recipients [52].

The non-inferiority of propiverine ER 45 mg once daily versus propiverine IR 15 mg three times daily was not demonstrated with regard to the primary endpoint of change from baseline in reflex volume (the maximum cystometric capacity was imputed for reflex volume if no uninhibited detrusor contractions occurred) (Table 6) [54]. The treatment difference for this endpoint was −12.4 mL (95 % confidence interval [CI] −58.9 to 34.0), and as the upper limit of the 95 % CI was not ≤25 mL, the predefined criteria for non-inferiority were not met. With regard to secondary efficacy parameters, there were no significant differences between treatment groups (Table 6). Interestingly, the proportion of patients experiencing incontinence reduced from 79 to 66 % in the propiverine IR group, and from 81 to 42 % in the propiverine ER group [54].

Propiverine 15 mg three times daily and oxybutynin 5 mg three times daily demonstrated generally similar efficacy in patients with symptoms resulting from NDO (Table 6) [55]. The maximum cystometric capacity and the maximum detrusor pressure (co-primary endpoints) improved significantly from baseline with both treatments (p values not reported), and in confirmatory analyses, propiverine was shown to be non-inferior to oxybutynin ($p = 0.011$ for maximum cystometric capacity and $p < 0.0001$ for maximum detrusor pressure). There were no significant differences between treatment groups for primary and secondary endpoints (Table 6) [55]. The mean volume voided at each void increased by 27 mL in the propiverine group (182 mL at baseline) and 37 mL in the oxybutynin group (206 mL at baseline), and the mean PVR increased by 68.3 versus 83.7 mL (baseline measures were 72.6 and 65.3 mL, respectively). Results in the per-protocol (as shown) and intent-to-treat populations for all endpoints were similar [55].

4.1.3 *In Men with Lower Urinary Tract Symptoms (LUTS)*

The efficacy of propiverine (10 or 20 mg once daily) in combination with an α_1-blocker was compared with an α_1-blocker alone in men with LUTS in several randomized, phase III studies [56–62]. Eligible patients were aged ≥50 years, with International Prostate Symptom Scores (IPSS) (screening tool evaluating seven symptoms and one HR-QOL item) or measures of bladder outlet obstruction indicative of BPE coexisting with symptoms of urinary frequency and/or urgency (Table 7) [56–58, 60, 61]. All studies were conducted over 4 weeks to 3 months. Selected inclusion and exclusion criteria and primary efficacy endpoints (where stated) are summarized in Table 7.

Overall, combination therapy with propiverine plus an α_1-blocker (including alfuzosin, tamsulosin, doxazosin, silodosin or naftopidil) was associated with generally similar or superior efficacy to that achieved with an α_1-blocker alone in men with LUTS/BPE (Table 8), and all treatment groups demonstrated significant improvements from baseline for most endpoints.

Combined therapy led to a significantly greater improvement in the storage IPSS than single-agent alfuzosin [56], doxazosin [57] or tamsulosin [58] (control groups) in three studies, including one in which storage IPSS was the primary endpoint [56], whereas other studies [60, 61] did not demonstrate a significant treatment difference for this endpoint (Table 8). The urgency severity IPSS item was also improved significantly ($p < 0.05$) more with combination therapy than with doxazosin [57] or tamsulosin [58] alone in two studies. Furthermore, storage functions, including the first desire to void and the maximum cystometric capacity, as well as detrusor overactivity,

Table 6 The efficacy of propiverine in adults with neurogenic detrusor overactivity. Results are from randomized, double-blind, multicentre studies. Analyses were performed in the intent-to-treat [52, 53] or per-protocol population [54, 55]

Study (duration)	Treatment (mg)	No. of pts	Mean change from BL									
			MCC (mL)		MDP (cmH_2O)		DC (mL/cm H_2O)		No. voids/24 h		Incontinence episodes/24 h	
			BL	EP	BL	EP	BL	EP	BL	EP	BL	EP
Compared with PL												
Stöhrer et al. [52]	PRO 15 tid	60	262	+104***	80.7	−27.0***	16.6	+5.2				
(2 weeks)	PL	53	296	−7	91.7	+0.2	15.2	+2.0				
Takayasu et al. [53]	PRO 20 od	64	177	+48**			38.6	+16.0*		−2.9**[a]		−2.4**[a]
(2 weeks)	PL	60	172	+4			56.2	−18.9		−1.6[a]		−1.0[a]
PRO ER compared with PRO IR												
Stöhrer et al. [54][b]	PRO IR 15 tid	33	101	+102[c]	66.1	−20.0	56.5	+58.3				
(3 weeks)	PRO ER 45 od	33	90	+90[c]	67.0	−20.0	52.1	+32.9				
Compared with OXY												
Stöhrer et al. [55]	PRO 15 tid	46	198	+111[c]	56.8	−19.0[c]	10.8	+11.9	10.9	−2.9	3.9	−1.6
(3 weeks)	OXY 5 tid	45	164	+134[c]	68.6	−25.5[c]	12.7	+25.1	12.0	−2.5	3.3	−1.3

BL baseline, *DC* detrusor compliance, *EP* endpoint, *ER* extended release, *IR* immediate release, *MCC* maximum cystometric capacity, *MDP* maximum detrusor pressure, *od* once daily, *OXY* oxybutynin, *PL* placebo, *PRO* propiverine, *tid* three times daily

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.0001$ vs. PL

[a] Values taken from a figure

[b] Reported in an abstract. The primary endpoint was the change from BL in reflex volume, with MCC imputed for reflex volume if no uninhibited detrusor contractions occurred

[c] Primary or co-primary endpoint

Table 7 Selected baseline characteristics, inclusion and exclusion criteria in key clinical trials evaluating propiverine as add-on therapy to an α_1-adrenoceptor antagonist in men aged ≥50 years with lower urinary tract symptoms and benign prostatic enlargement

Reference	Trial design	Mean age (≈years)	Key inclusion criteria	Selected exclusion criteria	Primary endpoint
Bae et al. [56]	r, sb, mc	63	IPSS ≥12; IPSS storage subscore ≥4	PVR ≥200 mL; urinary retention; prostate cancer	IPSS storage subscore
Lee et al. [57]	r, db, mc	66	≥1 urgency episode/24 h; ≥8 voids/24 h; urodynamically proven BOO (AG score ≥20)	PVR >30 % of MCC; prostate cancer	Voids/24 h
Matsukawa et al. [62][a]	r, sc	70	Previously untreated BPE; ≥1 urgency episode/7 days; OABSS ≥3		
Nishizawa et al. [58]	r, nb, mc	70	IPSS ≥8; ≥1 urgency episode/24 h; ≥8 voids/24 h	PVR >100 mL; Q_{max} <5 mL/s in total void >150 mL; prostate cancer	Voids/24 h
Seo et al. [60]	r, nb, sc	67	Prostate volume ≥20 mL; total IPSS ≥8	PVR >100 mL	
Yokoyama et al. [61]	r, nb, mc	69	Total IPSS ≥8; ≥1 urgency episode/24 h; ≥8 voids/24 h; PVR ≤50 mL		

AG Abrams-Griffith, *BOO* bladder outlet obstruction, *BPE* benign prostatic enlargement, *db* double-blind, *IPSS* International Prostate Symptom Score, *mc* multicentre, *MCC* maximum cystometric bladder capacity, *nb* non-blind, *OABSS* overactive bladder symptom score, *PVR* post-void residual urine, Q_{max} maximum flow rate, *r* randomized, *sb* single blind, *sc* single centre

[a] Reported in an abstract

were improved significantly ($p < 0.05$ for all) more with propiverine plus silodosin (reported in an abstract and dosages were not stated) than with silodosin alone [62].

In the study by Yokoyama et al. [61], differences between combination and monotherapy groups did not reach significance for any of the IPSS item scores. Propiverine 20 mg once daily plus naftopidil 50 mg once daily significantly improved incomplete emptying ($p < 0.01$), frequency ($p < 0.01$), urgency ($p < 0.0001$), weak stream ($p < 0.01$) and nocturia ($p < 0.01$) from baseline, whereas naftopidil

Table 8 Efficacy of propiverine as add-on therapy to an α_1-adrenoceptor antagonist in patients with lower urinary tract symptoms and benign prostatic enlargement. Results are from randomized trials and, where specified, analyses were performed in the full analysis set populations [56–58]

Study (duration)	Treatment (mg od)	No. of pts	Results (change from baseline)									
			IPSS storage		IPSS total		Voids/24 h		Q_{max} (mL/s)		PVR (mL)	
			BL	EP	BL	EP	BL	EP	BL	EP	BL	EP
Bae et al. [56]	PRO 10 + ALF 10	132	10.0	−4.0**[a]	23.2	−8.3*			14.7	+7.1	41.7	−15.6
(2 months)	ALF 10	77	8.1	−3.4[a]	19.0	−7.8			15.1	+5.8	44.0	−11.2
Lee et al. [57]	PRO 20 + DOX 4	142	9.2	−3.8*	22.0	−7.4	11.0	−2.6**[a]	10.4	+1.0	28.8	+20.8**
(8 weeks)	DOX 4	69	8.9	−2.9	20.6	−7.3	10.7	−1.6[a]	10.5	+1.7	30.8	−4.7
Matsukawa et al. [62][b]	PRO + SIL	54			18.5	−7.0			8.5	+1.3	44.0	+22.0*
(8 weeks)	SIL	52			18.3	−5.5			8.6	+2.3	59.0	−26.0
Nishizawa et al. [58][c]	PRO 10 + TAM 0.2	60		−2.2*[d]			11.3	−1.89*[a]			29.9	+25.0[d]
(12 weeks)	PRO 20 + TAM 0.2	62		−2.2*[d]			11.3	−1.20[a]			30.6	+30.0*[d]
	TAM 0.2	60		−1.1[d]			11.3	−0.82[a]			26.1	+12.0[d]
Saito et al. [59]	PRO 20 + TAM 0.2	67				−5.01		−3.06	11.3	+0.5	41.4	+24.0
(4 weeks)	TAM 0.2	46				−5.51		−2.52	11.5	+2.9	45.4	−9.5
Seo et al. [60]	PRO 10 + TAM 0.2	70	9.9	−3.8	21.9	−8.4			10.4	+2.7	37.1	−11.3
(3 months)	TAM 0.2	45	9.6	−3.0	21.1	−7.9			11.3	+2.9	34.3	−12.2
Yokoyama et al. [61]	PRO 20 + NAF 50	21	9.3	−3.4	17.9	−5.4	11.1	−2.0	10.2	+2.0	12.3	+28.9**[d]
(4 weeks)	PRO 20	18	9.6	−1.9	18.2	−2.1	12.4	−2.0	9.5	−0.5	10.8	+28.7*[d]
	NAF 50	19	10.3	−2.9	18.2	−4.9	12.7	−1.4	9.8	+0.9	16.7	−8.2[d]

ALF alfuzosin, *BL* baseline, *DOX* doxazosin controlled release gastrointestinal therapeutic system formulation, *EP* endpoint, *IPSS* international prostate symptom score, *NAF* naftopidil, *od* once daily, *PRO* propiverine, *pts* patients, *PVR* post-void residual urine, *Qmax* maximum flow rate, *SIL* silodosin, *TAM* tamsulosin

* $p < 0.05$, ** $p < 0.005$ vs. single-agent control

[a] Primary endpoint

[b] Reported in an abstract. Dosages not defined

[c] Prior to randomization, eligible patients received TAM 0.2 mg od alone for 8 weeks

[d] Values taken from a figure

alone significantly improved these same scores ($p < 0.05$) except for weak stream, and propiverine alone significantly improved only frequency and urgency ($p < 0.05$).

With regard to results from bladder diaries, combined therapy was associated with a significantly greater reduction in voids per 24 h (primary endpoint) than doxazosin [57] or tamsulosin [58] in two studies (Table 8). One of these studies [58] also demonstrated a significantly ($p < 0.01$) greater decrease in urgency episodes per 24 h with propiverine 10 mg once daily plus tamsulosin than with tamsulosin alone, but the difference between propiverine 20 mg once daily plus tamsulosin and tamsulosin alone did not reach significance for this endpoint. While the difference between treatment groups in voids per 24 h did not reach significance in the study by Saito et al. [59] (Table 8), nighttime voids were reduced significantly ($p = 0.0038$) more with combination therapy than with tamsulosin alone.

Combination therapy did not increase the mean maximum flow rate (Q_{max}) significantly more than single-agent α_1-blocker therapy in any randomized study (Table 8). In contrast, the increase in PVR (21–30 mL) was significantly ($p < 0.05$) greater in combination therapy groups than in control groups when the dose of propiverine in the combination arm was 20 mg once daily [57, 58, 61] (except for the study by Saito et al. [59] [$p = 0.065$]), but the change in PVR when propiverine 10 mg once daily was used in the combination arm was not significantly greater than that with control (Table 8) [56, 58, 60].

HR-QOL or patient satisfaction were improved to a similar extent in combination therapy and control arms in most studies [56, 58, 61, 62]. However, one study demonstrated a significantly ($p < 0.05$) greater improvement in the QOL IPSS item with combination therapy than with single-agent tamsulosin [60], and another study found that patient global satisfaction was significantly ($p = 0.014$) better with combination therapy, with an odds ratio (OR) for treatment benefit versus doxazosin alone of 2.34 (95 % CI 1.21 to 4.52) [57].

Non-randomized trials support results of randomized studies demonstrating that the addition of propiverine to an α_1-blocker for the treatment of OAB symptoms may be beneficial in some patients [63, 64]. For example, in a prospective, 12-week, observational study of >1,800 men with OAB (mean age of 66 years and prostate volume <40 mL) who were treated with propiverine ER 30 mg once daily alone or as add-on therapy with an α_1-blocker and stratified according to Q_{max}, OAB symptoms improved significantly ($p < 0.001$) from baseline in both treatment groups irrespective of baseline Q_{max} [64]. However, in patients with a Q_{max} of <15 mL/s, combined therapy was associated with a significantly ($p < 0.001$) greater IPSS improvement than an α_1-blocker alone.

4.2 Children and Adolescents

4.2.1 In Patients with IDO/OAB

Studies in children and adolescents with IDO/OAB include a randomized, double-blind, multicentre study [49] and two retrospective analyses [65, 66].

The randomized study was conducted over 8 weeks and compared the efficacy of propiverine 20 or 30 mg/day (dosage was adjusted for body weight and was administered in two divided doses) with that of placebo in children aged 5–10 years [49]. Children with a body weight of 17–46 kg, a micturition frequency of ≥8 per day and ≥1 episode of incontinence in 7 days were eligible to enter. A bladder capacity greater than that expected for age and a PVR >10 mL were among exclusion criteria [49].

The study comprised a wash-out phase and a 3-week run-in prior to randomization [49]. At the start of the run-in period, baseline urological parameters were re-examined and detailed lifestyle advice (urotherapy) was provided according to the International Children's Continence Society. The mean age of study participants was 7 years, and 42 % were female. Efficacy was assessed by questioning regarding voiding behaviour and based on a 3-day bladder diary.

The primary efficacy endpoint was the change in the number of voids in 24 h, which was improved significantly ($p < 0.001$) more with propiverine than with placebo (Table 4) [49]. Similarly, incontinence episodes per day (Table 4) and the mean increase in the volume voided at each void (31.4 mL [103 mL at baseline] vs. 5.1 mL [100 mL], respectively; $p < 0.0001$) improved significantly more with propiverine.

A subjective final evaluation of efficacy by the investigator rated the response to treatment as being 'good' or 'very good' in 64 % of propiverine recipients versus 33 % of placebo recipients (level of significance not reported) [49]. Similar results were reported in assessments made by the children and their parents.

In a retrospective review of 68 children (aged 3–10 years) with OAB (18 % had urgency incontinence) treated with propiverine 10 or 20 mg/day for at least 2 weeks (median duration 7.5 weeks) at a single centre in Korea, daytime voiding frequency was reduced from a median of 14 at baseline to 8.5 following treatment ($p < 0.05$) [65]. The overall response rate based on symptoms was 86.8 %, and in groups with and without urgency incontinence, the respective response rates were 83.3 and 88.0 % [65].

Propiverine and oxybutynin effectively managed urgency incontinence due to OAB in children aged 5–14 years in a retrospective, observational cohort study indicative of 'real-life' clinical practice in Europe [66]. After receiving propiverine 15.1–15.5 mg/day ($n = 437$) or oxybutynin 9.6–9.8 mg/day ($n = 184$), continence was achieved (primary endpoint) in 61.6 versus 58.7 % of patients. Thus, propiverine was shown to be non-inferior to oxybutynin, with an OR for achieving continence of 1.127 (95 % CI 0.793 to −) [66].

Furthermore, this study demonstrated that clinically relevant decreases in incontinence episodes per week (4.4 vs. 5.1) and voiding frequency per day (2.6 vs. 2.6) were not significantly different in the propiverine and oxybutynin treatment groups, but the mean time to achieve continence (186 vs. 259 days) and the mean duration of treatment (208 vs. 303 days) were significantly shorter with propiverine than oxybutynin ($p \leq 0.001$ for both) [66]. An analysis of the effect of independent variables on outcome demonstrated that higher levels of incontinence at baseline were associated with lower continence rates ($p < 0.001$) and an older age was associated with higher continence rates ($p = 0.018$).

4.2.2 In Patients with NDO

Propiverine effectively improved urodynamic assessments of NDO in short- (3–6 months) [67] and long-term (follow-up of up to 5.9 years, mean 3.6 years) [34] non-comparative, prospective studies and in two retrospective analyses [68, 69] in children and adolescents.

The short- ($n = 20$) [67] and long-term ($n = 17$) [34] prospective studies included patients aged <1 to 18 years, with a mean age of 8.9 years in the short-term study and 13 years at the last follow-up visit in the long-term study. All patients had urodynamically confirmed NDO (≈85 % of patients in each study had myelomeningocele) and most managed their micturition with clean intermittent catheterization. Propiverine was administered (first-line therapy in all but one patient [34]) using a body weight adapted dose (range of 0.23–1.58 mg/kg/day; 0.8 mg/kg/day is

recommended [70]). The primary efficacy outcomes comprised urodynamic variables [34, 67].

Propiverine treatment significantly reduced maximum detrusor pressure (by 12 cmH_2O over the short term [67] and by 19 cmH_2O over the long term [34]) and increased maximum cystometric capacity (by 65.9 and 106.8 mL, respectively) compared with baseline (Fig. 1).

In addition, propiverine significantly increased bladder compliance by 19 (baseline measure 11.2) mL/cmH_2O over the short term ($p < 0.01$) [67]. In the short-term study, reflex volume (volume at first detrusor contraction) was significantly increased by 71 (baseline measure 103.8) mL ($p < 0.005$), and the incontinence score (scale of 0–3, with a score of 0 indicating no incontinence) was also significantly improved from 2.42 at baseline to 1.62 after treatment ($p < 0.05$) [67]. Similarly, over long-term propiverine treatment, the incontinence score improved significantly from 2.2 to 1.2 ($p = 0.05$), which corresponds with an incontinence episode occurring about once in 24 h (usually at night); nine (53 %) children became dry [34]. The detrusor leak point pressure was also assessed over long-term treatment, reducing by 9.7 cmH_2O from a baseline measure of 44.7 cmH_2O [34]. At the final assessment, ultrasonography of the upper urinary tract revealed that 14 children had normal or slightly dilated kidneys [34]. There were no significant differences between pre- and post-treatment levels of hydronephrosis.

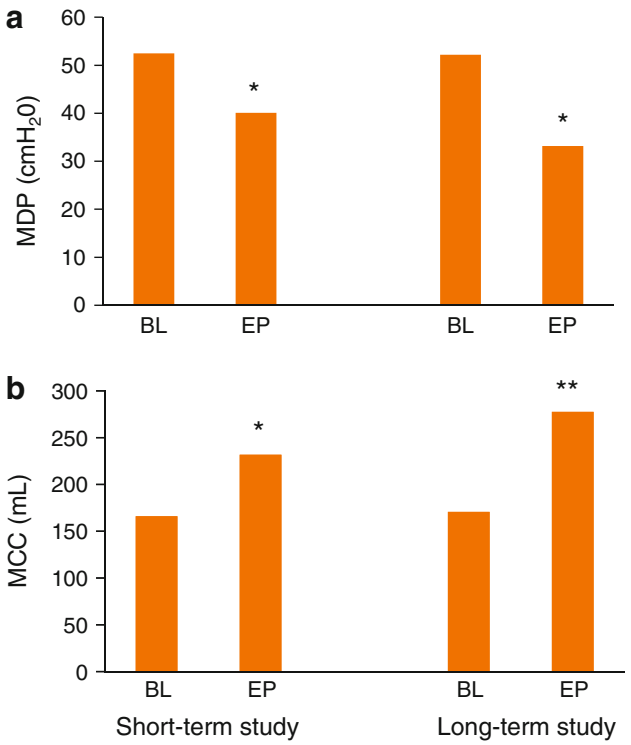

Fig. 1 Efficacy of propiverine in children and adolescents with neurogenic detrusor overactivity. Results from two prospective studies conducted over 3–6 months (short-term study; $n = 20$) [67] and a mean of 3.6 years (long-term study; $n = 17$) [34] show the mean improvement from baseline in maximum detrusor pressure (**a**) and maximum cystometric capacity (**b**). *BL* baseline, *EP* endpoint, *MCC* maximum cystometric capacity, *MDP* maximum detrusor pressure. * $p < 0.05$, ** $p < 0.005$ vs. BL

Although results from non-randomized studies must be viewed with caution, propiverine demonstrated superior efficacy to oxybutynin in a retrospective analysis that compared outcomes in 255 children and adolescents aged 1–18 (mean 7.5) years treated in 14 specialized centres throughout Germany with variable doses of either agent for at least 12 months [69]. The proportion of patients who achieved a maximum detrusor pressure of ≤40 cmH_2O or a total reduction in maximum detrusor pressure of >50 % of pretreatment values (primary outcome) was significantly higher in the propiverine group than in the oxybutynin group (74.2 vs. 49.6 %; $p < 0.0005$) [69]. According to prespecified hypotheses, the non-inferiority then subsequent superiority of propiverine versus oxybutynin was confirmed, with an unadjusted OR of achieving the primary outcome of 2.92 (95 % CI 1.544 to 5.588).

With regard to secondary endpoints in this analysis [69], propiverine increased maximum cystometric capacity (96.4 vs. 88.2 mL) and decreased maximum detrusor pressure (23.1 vs. 10.2 mL) significantly more than oxybutynin ($p = 0.001$ for both). The proportion of continent patients increased from 7.7 to 31.5 % in the propiverine group and from 20.8 to 50.4 % in the oxybutynin group. Improvements in vesicoureteral reflux occurred with both propiverine and oxybutynin, and there was no significant difference between treatment groups [69].

A retrospective review of data from 74 children and adolescents aged 11 months to 19 years with congenital or traumatic NDO treated with propiverine (5–75 mg/day) at four centres in Germany for a mean duration of 2 years and 4 months revealed significant improvements from baseline in maximum cystometric capacity, maximum detrusor pressure and bladder compliance ($p < 0.001$ for all) [68].

5 Tolerability

5.1 Adults

5.1.1 General Profile

In Patients with IDO/OAB and NDO: Propiverine was generally well tolerated in randomized clinical trials in adults (including elderly patients) with IDO/OAB [36–41, 43–45] or NDO [52, 54, 55]. Across all studies, adverse events associated with propiverine (20–45 mg/day for up to 12 weeks) were generally mild to moderate in severity and typical of all antimuscarinic agents, the most frequent of

which were dry mouth (2.0–53.0 %), constipation (3.0–17 %) and blurred vision/abnormal vision (0.3–33.0 %) [36–41, 43–45, 52, 55].

In a large (n = 988) study comparing propiverine IR 15 mg twice daily and ER 30 mg once daily with placebo in patients with IDO/OAB, adverse events were reported by 39, 34 and 20 % of patients, respectively (Fig. 2 illustrates the incidence of the most frequent events), and severe adverse events occurred in 3.8, 2.8 and 0 % [38]. Treatment withdrawal (6 % of patients across all groups) resulted most commonly from gastrointestinal disorders [38]. Overall, ≥80 % of investigators and patients rated tolerability as being 'good' or 'very good' [38].

Compared with propiverine IR 15 mg three times daily, propiverine ER 45 mg once daily appeared to have a more favourable tolerability profile in patients with NDO (as reported in an abstract; levels of significance were not reported) [54]. In the propiverine IR and ER groups, 48.5 versus 36.4 % of patients, respectively, experienced at least one adverse event. Dry mouth was reported in 24.2 versus 27.3 % of patients, gastrointestinal motility disorders occurred in 9.1 versus 3.0 % and accommodation disorders occurred in 6.1 versus 0 % [54].

The tolerability profiles of propiverine and tolterodine were generally similar in two studies in patients with IDO/OAB [42, 44]. In the study comparing the ER formulations of each agent (i.e. propiverine ER 30 mg once daily versus tolterodine ER 4 mg once daily), the incidence of adverse events was 41 versus 45 %, respectively [42]. In Japanese patients with OAB, propiverine 20 mg once daily was associated with a higher incidence of adverse events than imidafenacin 0.1 mg twice daily (82 vs. 73 % of patients; p = 0.01); in the placebo group, 68 % of patients reported adverse events [40]. Compared with oxybutynin 5 mg three times daily, propiverine 15 mg three times daily was shown to have non-inferior, equivalent tolerability ($p < 0.0001$) in patients with NDO [55]. The proportion of patients experiencing anticholinergic adverse events (co-primary endpoint) was 63.0 % with propiverine versus 77.8 % with oxybutynin [55].

While dry mouth is common to all antimuscarinic therapies, the incidence varied between active treatments and was dose dependent in clinical trials. Overall, propiverine 20–45 mg/day was associated with a lower incidence of dry mouth than oxybutynin 10–15 mg/day [43, 45, 55] and solifenacin 10 mg/day [41], a higher incidence than imidafenacin 0.2 mg/day [40] and solifenacin 5 mg/day [41], and a similar incidence to tolterodine (2 mg twice daily [44] or ER 4 mg once daily [42]). In a placebo-controlled, crossover study [43], the effect of propiverine 20 or 45 mg/day on salivary flow rate was significantly lower than that of oxybutynin 15 mg/day ($p < 0.0001$ for both), with a corresponding lower incidence of dry mouth in the propiverine treatment groups (34 and 52 vs. 83 %, respectively); the incidence of dry mouth in the placebo group was 17 % [43]. Similarly, in another study in patients with IDO/OAB [45] and one in patients with NDO [55], there was a significantly lower incidence of dry mouth with propiverine 15 mg three times daily than with oxybutynin 5 mg two (p = 0.022) [45] or three times daily (p = 0.02) [55] and, in one of these studies [45], dry mouth was less severe with propiverine. In contrast, the incidence of dry mouth associated with propiverine 20 mg once daily was greater than with imidafenacin 0.1 mg twice daily (39.9 vs. 31.5 %; p = 0.03 [13.8 % with placebo]) and more severe than with imidafenacin ($p < 0.05$) [40]. In another study, the incidence of dry mouth associated with propiverine 20 mg once daily was greater than with

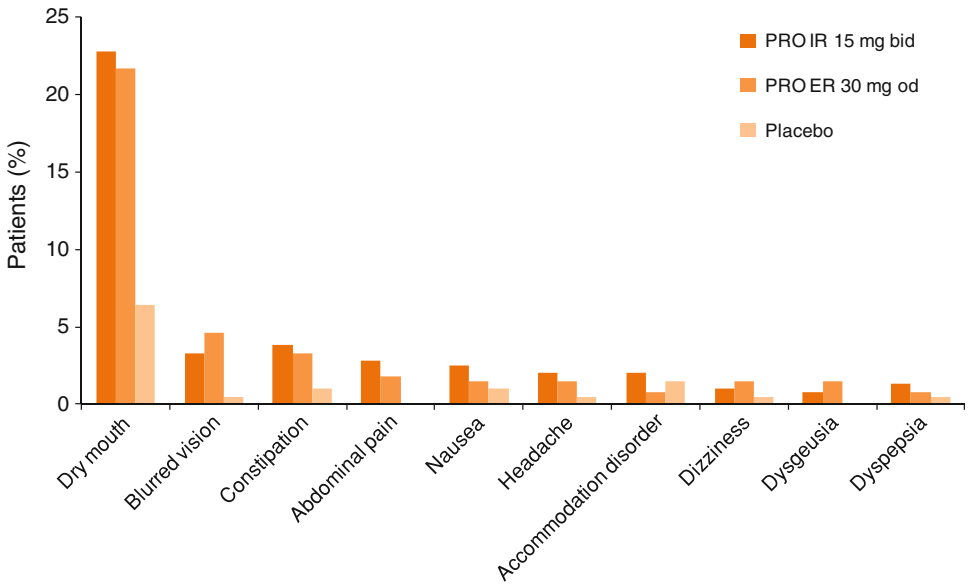

Fig. 2 Tolerability of propiverine in patients with idiopathic detrusor overactivity/overactive bladder. Results are from a randomized, double-blind study in 988 patients (safety population) treated with propiverine immediate release or extended release or placebo for 32 days [38]. *bid* twice daily, *ER* extended release, *IR* immediate release, *od* once daily, *PRO* propiverine

solifenacin 5 mg once daily (25.8 vs. 16.9 %; $p < 0.01$), but lower than solifenacin 10 mg once daily (25.8 vs. 34.1 %; $p = 0.012$) (the incidence with placebo was 5.7 %) [41]. In the study comparing propiverine 15 mg twice daily and tolterodine 2 mg twice daily [44], dry mouth occurred in 20 and 19 % of patients, respectively.

In a crossover study, visual near point was increased with propiverine 20 and 45 mg/day and oxybutynin 15 mg/day, and the difference between groups was not significant [43]. In this study, abnormal vision was reported in 24, 33 and 22 % of patients, respectively, and in 0 % of patients in the placebo group [43]. In patients with NDO, 20 % of patients receiving propiverine 15 mg three times daily versus 10 % of patients receiving oxybutynin 5 mg three times daily reported vision changes [55]. Eye disorders (including accommodation disorders, blurred vision, setback of eyesight, loss of viscus and pain in eye balls) were reported in 9 % of patients receiving propiverine 15 mg twice daily and 7 % of patients receiving tolterodine 2 mg twice daily [44]. In studies comparing propiverine 20 mg once daily with solifenacin 5 or 10 mg once daily [41], or imidafenacin 0.1 mg twice daily [40], blurred vision was mild in most cases, and the incidence was not significantly different between treatment groups.

Where stated across all studies in patients with IDO/OAB and NDO, propiverine was not associated with any clinically important changes in laboratory tests [36–38, 40, 41, 44, 52].

Results from two large observational studies in patients with OAB in clinical practice in Germany also demonstrated that propiverine therapy was generally well tolerated [50, 51]. Dry mouth was the most frequent adverse event in both analyses [50, 51], and in one study ($n = 5565$) [50], the incidence decreased from 16.5 % after 4 weeks of propiverine ER treatment to 13.6 % after 12 weeks of treatment, suggesting that dry mouth may resolve in some patients with continued therapy. In addition, long-term treatment with propiverine for up to 1 year was generally well tolerated in patients ($n = 141$) with OAB symptoms in Japan [71]. Adverse effects occurred in 15.6 % of patients, and the most common events were dry mouth (4 %), constipation (3 %) and dysuria (3 %).

In Men with LUTS: Once-daily propiverine 10 or 20 mg in combination with an α_1-blocker in men with LUTS/BPE was generally well tolerated, but the combination regimen was associated with a higher incidence of adverse events than an α_1-blocker alone [56–62]. For example, in the Korean study by Lee et al. [57], adverse events occurred in 42.7 % of patients receiving once-daily propiverine 20 mg plus doxazosin 4 mg compared with 18.9 % of patients receiving doxazosin alone ($p < 0.05$) [57]. In a second Korean study comparing once-daily propiverine 10 mg plus alfuzosin 10 mg with once-daily alfuzosin alone, the incidence of adverse events in the respective groups was 6.8 versus 3.8 % [56]. In both studies the majority of events were mild/minor (85 [57] and 75 % [56]).

As demonstrated in patients with IDO/OAB and NDO, mild antimuscarinic adverse events, in particular dry mouth (1.5–18.3 %), were the most frequently reported [56–58]. An additional adverse effect associated with propiverine add-on treatment in this patient population, which was not generally reported in other populations, was that of voiding difficulty. For example, in the study by Bae et al. [56], voiding difficulty (including post-void tenesmus, straining, hesitancy and terminal dribbling) was reported in 6 of 132 (4.5 %) patients receiving once-daily propiverine 10 mg plus alfuzosin 10 mg compared with 1 of 77 (1.3 %) patients receiving alfuzosin alone (p value not reported). There were no reports of treatment discontinuation due to adverse events in this study [56].

In contrast, treatment discontinuation due to adverse events (dry mouth, increased PVR and constipation) occurred in 7 of 142 (4.9 %) patients receiving once-daily propiverine 20 mg plus doxazosin 4 mg compared with 1 of 69 (1.5 %) patients receiving doxazosin alone [57]. There was one case of acute urinary retention in the group of patients receiving propiverine 20 mg plus tamsulosin 0.2 mg, but no cases were reported in the group receiving propiverine 10 mg add-on therapy in this study [58].

5.1.2 *Cardiovascular Effects*

Propiverine treatment was not associated with arrhythmias in 98 elderly patients (aged ≥60 years) treated with propiverine 15 mg three times daily (≈47 % were receiving concomitant cardiovascular medication) [37]. During a standard ECG, there were no significant changes compared with baseline or placebo in QTc or heart rate [37]. However, during a 24-h ECG recording, propiverine was associated with a significantly ($p < 0.001$) increased minimum heart rate compared with placebo, but the difference versus placebo in the effect on maximum heart rate was not significant. The frequency of cardiac adverse events (Lown classes IVa/b) was random across both groups and was not significantly different between propiverine or placebo treatment groups [37]. See Section 2 for additional data regarding the cardiovascular effects of propiverine.

In a crossover study [43], propiverine 20 or 45 mg/day increased heart rate from baseline by a mean of ≈3 beats/min, whereas oxybutynin 15 mg/day decreased heart rate by a mean of ≈5 beats/min ($p < 0.0001$); placebo was associated with a reduction in mean heart rate of ≈2 beats/min. Propiverine (both dosages) had a greater effect on heart rate variability than oxybutynin, as determined by St George's index ($p < 0.05$) and the PNN50 (measure of difference between successive R–R intervals that were

>50 milliseconds) ($p < 0.0001$) during full 24-h ECG recordings [43].

Propiverine 20 mg once daily was associated with a significant increase from baseline in heart rate by a mean of 4.4 beats/min ($p < 0.0001$), whereas heart rate was not changed significantly with imidafenacin 0.1 mg (−0.8) or placebo (−1.0) [40]. There was no evidence of arrhythmia or clinical arrhythmic events in any treatment groups [40].

5.2 Children and Adolescents

Propiverine was generally well tolerated in clinical trials in children and adolescents with IDO/OAB [49] or NDO [34, 67].

In 171 children aged 5–10 years with IDO/OAB who received propiverine 10–30 mg/day for 8 weeks, adverse events were reported in 23 % of patients receiving propiverine versus 20 % of patients receiving placebo [49]. Adverse events belonging to the infections and infestations class (13.8 vs. 15.5 %, respectively) were the most commonly reported, including influenza (4.6 vs. 1.2 %) and urinary tract infection (2.3 vs. 1.2 %). Dry mouth (3.4 %), abdominal pain (3.4 %), constipation (2.3 %), accommodation disorder (2.3 %) and headache (2.3 %) were all reported in propiverine-treated patients but not in patients receiving placebo [49]. All adverse events were rated as mild or moderate, except for one case of abdominal pain (propiverine group) and one case of acute bronchitis (placebo group). Two patients receiving propiverine and one receiving placebo discontinued treatment due to adverse events, although relationship to treatment was not certain [49]. Propiverine was not associated with urinary retention or any clinically important changes in blood pressure, pulse rate or ECG. Investigators rated overall tolerability as 'good' or 'very good' in 96.6 versus 96.4 % of patients receiving propiverine or placebo [49].

In children and adolescents with NDO receiving propiverine ($\approx$0.8 mg/kg/day) in a prospective, non-comparative analysis, adverse events were uncommon [34, 67]. At 3- to 6-month follow-up, 10 % of patients reported adverse events [67]. At a mean follow-up of 3.6 years, all events were mild or moderate in severity and overall tolerability was rated as 1.3, according to a tolerability score (scale of 1–4, with 1 very good and 4 insufficient) [34]. No patients discontinued propiverine prematurely.

Retrospective, observational studies in children aged 5–14 years with IDO and urgency incontinence ($n = 621$) [66] and children and adolescents aged 1–18 years with NDO ($n = 255$) [69] indicated that propiverine has a more favourable tolerability profile than oxybutynin. Patients with IDO and urgency incontinence were treated for a mean of 208 and 303 days, respectively, and the incidence of adverse events (primary tolerability outcome) was significantly lower with propiverine 15.1–15.5 mg/day than with oxybutynin 9.6–9.8 mg/day (3.9 vs. 16.3 %; $p < 0.001$). Dry mouth was reported in 3 versus 6.2 % of patients, respectively [66]. Similarly, in patients with NDO treated with variable dosages of propiverine or oxybutynin for $\geq$12 months, adverse events were reported in 10.2 versus 26.5 % of patients [69]. While this treatment difference did not reach significance, the incidence of adverse events was significantly lower with propiverine in the subgroup of patients with myelomeningocele ($p = 0.01$).

6 Dosage and Administration

Propiverine is indicated for the treatment of urinary incontinence and/or urinary frequency and urgency in patients with OAB symptoms or NDO [28, 29, 70, 72, 73]. The drug is available in several different formulations worldwide. For adult use in Europe and most other countries, propiverine is available as IR tablets containing 15 mg (Mictonorm®, Detrunorm®) and as ER capsules containing 30 or 45 mg (Mictonorm Uno®, Detrunorm® XL) [28, 29, 72, 73]. In Europe, the recommended dose in adults is one propiverine IR 15 mg tablet twice daily, although once daily may be sufficient in some patients and the dosage may be increased to three times daily if necessary [28], or one propiverine ER 30 [29] or 45 [72] mg capsule once daily. The daily regimen of propiverine IR 15 mg three times daily may be replaced by propiverine ER 45 mg once daily as indicated [72]. In patients with NDO, a higher dose is generally required; the maximum recommended daily dose in adults is propiverine 45 mg [28, 29, 72, 73]. In Japan and Korea, propiverine is available as IR film-coated tablets at doses of 10 or 20 mg (BUP-4®), which are usually administered once daily.

In children, the recommended average daily dose is 0.8 mg/kg administered in two or three divided doses using propiverine 5 mg tablets (Mictonetten®) [70]. It is recommended that children with a body weight greater than 35 kg receive the standard adult dose of 15 mg twice daily [70].

In clinical trials in men with LUTS, propiverine 10 or 20 mg once daily was coadministered with an α_1-blocker to control urinary storage symptoms (Section 4.1.3).

There is no need for the dose of propiverine to be adjusted in elderly patients or in those with mild to moderate renal impairment (Section 2). In patients with mild hepatic impairment, propiverine should be used with caution, and the drug is not recommended for use in patients with moderate to severe hepatic impairment as no data are available in this population [29]. Propiverine should not be given during pregnancy [28].

As with all anticholinergic agents, propiverine may induce mydriasis, and in patients with narrow angles of the anterior chamber, the risk of acute angle-closure glaucoma may be increased [29]. It is possible that symptoms of prostatic hypertrophy and severe congestive heart failure may be aggravated following administration of propiverine [29]. Local prescribing information should be consulted for full details regarding indications, dosages, contraindications, warnings and precautions.

7 Place of Propiverine in the Management of Patients with OAB Associated with IDO or NDO, and in Men with LUTS

The assessment of patients with urinary symptoms suggestive of detrusor overactivity will differ between those with an idiopathic or neurological underlying cause. In patients with IDO/OAB, diagnosis is generally based on clinical symptoms [11, 12]. Urodynamic studies may be helpful to clarify the treatment plan or exclude other disorders, but are not always necessary for diagnosis or for commencing therapy [11, 12]. First-line treatment consists of behavioural therapy, including bladder training, bladder control strategies, pelvic floor muscle training and fluid management [11, 12]. In adults, antimuscarinic therapy is recommended for first-line use in combination with behavioural therapy as indicated, or commenced if symptoms persist after the initiation of behavioural therapy [11, 12]. In children, antimuscarinic treatment should be commenced only after standard conservative measures have been exhausted [74].

In patients with congenital or acquired neurological urinary tract dysfunction, diagnosis is based on a comprehensive assessment, including urodynamic tests [9]. In these patients, early diagnosis and treatment of NDO are important in order to manage bladder capacity and detrusor pressure and control urinary reflux to avoid irreversible damage to the upper urinary tract [9]. Antimuscarinic agents are the standard first-line pharmacological treatment in patients with NDO [9].

The diagnosis of BPE with detrusor overactivity in men with LUTS includes a comprehensive range of assessments, including ultrasound and uroflowmetry, and should exclude other conditions that could cause LUTS [75]. As with IDO/OAB, a conservative approach to treatment may be warranted initially if the patient is not too bothered by his or her symptoms [75]. The first-line pharmacological agent recommended in these patients is an α_1-blocker [75]. Guidelines also recommend that combination therapy with an α_1-blocker and an antimuscarinic agent be considered in patients with moderate to severe LUTS who do not respond to monotherapy [75]. However, care should be taken if significant bladder outlet obstruction is thought to be present, because of the risk of increasing PVR and urinary retention [75].

Antimuscarinic agents are well established for the treatment of urinary symptoms associated with detrusor overactivity, as they have been shown to consistently reduce symptoms and improve HR-QOL [9, 75, 76]. They act by blocking the action of acetylcholine at the muscarinic receptors in detrusor smooth muscle (Section 2), thereby suppressing involuntary bladder contractions. Of the commonly used antimuscarinic agents (including propiverine, darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine and trospium chloride), no particular drug is recommended over another in treatment guidelines for adults, but rather that treatment be individualized, with consideration given to the pharmacological profiles of different drugs together with patient co-morbidities and concomitant medications [9, 11, 12, 75]. However, in children, it is recommended that preference is given to antimuscarinic agents that have been shown to be well tolerated and effective (such as propiverine) over those that have not been evaluated specifically in children with OAB [74].

Unlike most other antimuscarinic agents, propiverine has a mixed action in the treatment of OAB [77]. As well as blocking muscarinic receptors in the detrusor muscle, propiverine inhibits calcium influx and modulates intracellular calcium, thereby diminishing muscle spasm (Section 2). There is also evidence to suggest that propiverine is associated with the reversal of ATP-induced bladder overactivity and may have antagonist effects at α_1 adrenoceptors (Section 2).

In well designed studies in adults with IDO/OAB, propiverine was significantly more effective than placebo, and similarly effective to other antimuscarinic agents, in improving urinary symptoms such as frequency, incontinence and urgency, as well as improving HR-QOL (Section 4.1.1). However, with regard to some endpoints in some studies, propiverine was more effective than tolterodine [42] or imidafenacin [40] and less effective than the high dose of solifenacin 10 mg [41].

Similarly, in adults with NDO, propiverine was significantly more effective than placebo, and demonstrated similar efficacy to that of oxybutynin, in improving endpoints such as bladder capacity and detrusor pressure, as well as reducing the number of incontinence episodes (Section 4.1.2).

In men with LUTS/BPE, combination therapy with propiverine plus an α_1-blocker was associated with generally similar or superior efficacy to that achieved with an α_1-blocker alone, as determined by improvements in IPSS storage and frequency and HR-QOL (Section 4.1.3). To date, the efficacy of add-on propiverine has not

been compared with that of add-on therapy with another antimuscarinic in this patient population. However, drug selection should be tailored to the patient, with particular consideration given to tolerability issues in this predominantly elderly population. Determining which patients with LUTS are most likely to benefit from combined therapy is an important consideration in clinical practice. There is clear evidence to show that men with predominantly bladder storage symptoms will benefit from combination therapy, but more data are needed to confirm the risks associated with the presence of varying degrees of bladder outlet obstruction [75]. In general, clinical studies with antimuscarinic agents (including propiverine; see Table 8) in men with LUTS have been associated with significant but small increases in PVR, which are not thought to be of clinical significance [78]. It has also been suggested that the α_1-blocking properties of propiverine may limit the risk of urinary retention in this patient population [64].

As shown in adults, the efficacy of propiverine in children and adolescents with IDO/OAB was significantly greater than that of placebo, and was non-inferior to that of oxybutynin (Section 4.2.1). However, propiverine was associated with a significantly faster time to achieve continence and a significantly reduced duration of treatment compared with oxybutynin. In children and adolescents with NDO, propiverine significantly improved urodynamic assessments, including bladder capacity and detrusor pressure, and levels of incontinence from baseline in short- (3–6 months) and long-term (mean 3.6 years) prospective studies (Section 4.2.2). In addition, in a retrospective study, propiverine was significantly more effective than oxybutynin, with significantly more propiverine-treated patients achieving a detrusor pressure of $\leq$40 cmH_2O (Section 4.2.2).

Propiverine is generally well tolerated, and in clinical studies in adults and children with IDO/OAB or NDO, or in men with LUTS/BPE, adverse events were mostly mild to moderate in severity and consistent with those associated with all antimuscarinic agents (Section 5). The most common adverse event is dry mouth and, overall in adults and children, propiverine was associated with a lower incidence than oxybutynin (Section 5.1.1). Although head-to-head prospective studies in children are lacking, data suggest that propiverine has a more favourable tolerability profile overall than oxybutynin in children with IDO/OAB or NDO (Section 5.2).

Because of propiverine's calcium antagonist properties, the cardiovascular effects of the drug have been investigated. Studies in healthy volunteers and in men with coronary heart disease found that propiverine had no negative effects on cardiac function with regard to QTc intervals derived from resting and exercise ECGs (Section 2). In clinical studies in patients with IDO/OAB, including a study in the elderly who received propiverine 45 mg/day, propiverine treatment was not associated with arrhythmias, but was generally associated with an increase in heart rate (Section 5.1.2). Furthermore, cardiac arrhythmias have not been reported with propiverine throughout more than three decades of clinical use [24]. The clinical significance of the increase in heart rate is unknown.

In head-to-head comparisons of propiverine IR and ER, the tolerability profile was not significantly different in a study in patients with IDO/OAB [38], but favoured propiverine ER in a study in patients with NDO [54]. The ER formulation of propiverine is associated with lower C_{max} values than the IR formulation (Section 3), which could be expected to improve tolerability and, in particular, anticholinergic adverse events such as dry mouth.

Muscarinic receptors in the brain play a role in cognitive function and, thus, antimuscarinic agents have the potential to cause central nervous system (CNS) adverse effects, which may be of particular concern in elderly patients. The level of CNS toxicity associated with a drug is likely to be dependent on its physiochemical properties, and in particular its ability to cross the blood brain barrier [79]. A recent systematic review and meta-analysis of clinical trials of antimuscarinic agents in the treatment of OAB found that more detailed, standardized CNS outcomes are needed in trials to adequately compare available therapies [79]. However, overall, data in adults indicated that of all antimuscarinic agents, oxybutynin is the most likely to penetrate the CNS and affect cognition [79].

Cognitive impairment was not reported in clinical trials of propiverine summarized in this review (Section 5). In a small study (reported in an abstract) in patients with neurological disease, including dementia and/or motor dysfunction, propiverine treatment improved symptoms of OAB and did not significantly affect cognitive performance or mental or motor function [80]. Similarly, in elderly dementia patients, the addition of propiverine 20 mg once daily to donepezil improved symptoms of OAB without any cognitive change [81]. Furthermore, significant impairment in psychomotor performance was not observed during propiverine treatment, in a well designed trial using a range of tests in healthy volunteers (also reported in an abstract) [82].

OAB can have a considerable impact on HR-QOL [83]. Not only can symptoms affect daily activities and productivity, but patients often have to deal with embarrassment and anxiety [83]. Furthermore, given the high prevalence of OAB (Section 1), associated costs place a huge burden on healthcare systems. Limited data are available to compare the cost utility of the various antimuscarinic agents in the treatment of OAB. A cost-utility analysis, performed from the UK National Health Service perspective, compared the cost effectiveness of

solifenacin with darifenacin, fesoterodine, oxybutynin, propiverine and tolterodine using a decision-tree model over 1 year [84]. Estimates of clinical effectiveness were based on a systematic review and meta-analysis [76]. The cost-utility analysis found that, overall, solifenacin was the most cost-effective agent (2007/2008 values) [84]. Unfortunately, it is difficult to fully reconcile the costs applied to propiverine in this analysis, as the model used propiverine 20 mg, which is not available in the UK or other European countries.

In conclusion, propiverine is a well established antimuscarinic agent with a mixed mode of action in the treatment of OAB. In adults with IDO/OAB, propiverine demonstrated similar efficacy to that of other antimuscarinic agents and, in adults with NDO, propiverine and oxybutynin demonstrated similar efficacy. Propiverine was generally well tolerated in these patient populations, with a lower incidence of dry mouth than that associated with oxybutynin. In men with LUTS/BPE, propiverine administered as add-on therapy to an α_1-blocker demonstrated similar or superior efficacy to that achieved with an α_1-blocker alone, and combination therapy was particularly effective in patients with urinary storage symptoms. Combination therapy was generally well tolerated, but was associated with a higher incidence of adverse events than an α_1-blocker alone. In children and adolescents with IDO/OAB or NDO, limited data show that propiverine was generally more effective and better tolerated than oxybutynin. Thus, propiverine provides a valuable option for the treatment of adults and children with OAB associated with IDO or NDO, and for add-on therapy with an α_1-blocker in men with storage LUTS.

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References

1. Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology of lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. Neurourol Urodyn. 2002;21(2):167–78.
2. Chapple C, Roehrborn CG. A shifted paradigm for the further understanding, evaluation, and treatment of lower urinary tract symptoms in men: focus on the bladder. Eur Urol. 2006;49(4):651–9.
3. Oelke M, Baard J, Wijkstra H, et al. Age and bladder outlet obstruction are independently associated with detrusor overactivity in patients with benign prostatic hyperplasia. Eur Urol. 2008;54(2):419–26.
4. Cheung WW, Blank W, Borawski D, et al. Prevalence of overactive bladder, its under-diagnosis, and risk factors in a male urologic veterans population. Int J Med Sci. 2010;7(6):391–4.
5. Stewart WF, Van Rooyen JB, Cundiff GW, et al. Prevalence and burden of overactive bladder in the United States. World J Urol. 2003;20(6):327–36.
6. Temml C, Heidler S, Ponholzer A, et al. Prevalence of the overactive bladder syndrome by applying the International Continence Society definition. Eur Urol. 2005;48(4):622–7.
7. Chung JM, Lee SD, Kang DI, et al. Prevalence and associated factors of overactive bladder in Korean children 5–13 years old: a nationwide multicentre study. Urology. 2009;73(1):63–9.
8. Kajiwara M, Inoue K, Kato M, et al. Nocturnal eneuresis and overactive bladder in children: an epidemiological study. Urology. 2006;13(1):36–41.
9. Stöhrer M, Blok B, Castro-Diaz D, et al. EAU guidelines on neurogenic lower urinary tract dysfunction. Eur Urol. 2009;56(1):81–8.
10. Wei JT, Calhoun E, Jacobsen SJ. Urologic diseases in America project: benign prostatic hyperplasia. J Urol. 2005;173(4):1256–61.
11. Lucas MG, Bosch JLHR, Cruz FR, et al. European Association of Urology. Guidelines on urinary incontinence (online). Available from URL: http://www.uroweb.org/fileadmin/guidelines/2012 [Accessed 2012 Sep 6].
12. Yamaguchi O, Nishizawa O, Takeda M, et al. Clinical guidelines for overactive bladder. Int J Urol. 2009;16(2):126–42.
13. Madersbacher H, Mürtz G. Efficacy, tolerability and safety profile of propiverine in the treatment of the overactive bladder (non-neurogenic and neurogenic). World J Urol. 2001;19(5):324–35.
14. Wuest M, Hecht J, Christ T, et al. Pharmacodynamics of propiverine and three of its main metabolites on detrusor contraction. Br J Pharmacol. 2005;145(5):608–19.
15. Wuest M, Weiss A, Waelbroeck M, et al. Propiverine and metabolites: differences in binding to muscarinic receptors and in functional models of detrusor contraction. Naunyn-Schmied Arch Pharmacol. 2006;374(2):87–97.
16. Yamada S, Ito Y, Taki Y, et al. The N-oxide metabolite contributes to bladder selectivity resulting from oral propiverine: muscarinic receptor binding and pharmacokinetics. Drug Metab Dispos. 2010;38(8):1314–21.
17. Uchida S, Kurosawa S, Fujino Oki T, et al. Binding activities by propiverine and its N-oxide metabolites of L-type calcium channel antagonist receptors in the rat bladder and brain. Life Sci. 2007;80(26):2454–60.
18. Propping S, Braeter M, Grimm M-O, et al. Anticholinergic effects of cis- and trans-isomers of two metabolites of propiverine. Naunyn-Schmied Arch Pharmacol. 2010;381(4):329–38.
19. Wuest M, Eichhorn B, Braeter M, et al. Muscarinic receptor expression and receptor-mediated detrusor contraction: comparison of juvenile and adult porcine tissue. Pflugers Arch. 2008;456(2):349–58.
20. Wuest M, Witte LP, Michel-Reher MB, et al. The muscarinic receptor antagonist propiverine exhibits α1-adrenoceptor antagonism in human prostate and porcine trigonum. World J Urol. 2011;29(2):149–55.
21. Moon HS, Lee JW, ParK SY, et al. Oxybutynin and propiverine suppress adenosine triphosphate-induced bladder overactivity other than through antimuscarinic mechanisms. Urology. 2010;76(2):509. (e8–12).
22. Scheepe JR, van den Hoek J, Jünemann KP, et al. A standardised mini pig model for in vivo investigations of anticholinergic effects on bladder function and salivation. Pharmacol Res. 2007;55(5):450–4.
23. Christ T, Wettwer E, Wuest M, et al. Electrophysiological profile of propiverine: relationship to cardiac risk. Naunyn-Schmied Arch Pharmacol. 2008;376(6):431–40.

24. Donath F, Braeter M, Feustel C. The influence of propiverine hydrochloride on cardiac repolarization in healthy women and cardiac male patients. Int J Clin Pharmacol Ther. 2011;49(6): 353–65.
25. Haustein KO, Huller G. On the pharmacokinetics and metabolism of propiverine in man. Eur J Drug Metab Pharmacokinet. 1988;13(2):81–90.
26. May K, Westphal K, Giessmann T, et al. Disposition and antimuscarinic effects of the urinary bladder spasmolytics propiverine: influence of dosage forms and circadian-time rhythms. J Clin Pharmacol. 2008;48(5):570–9.
27. May K, Giessmann T, Wegner D, et al. Oral absorption of propiverine solution and of the immediate and extended release dosage forms: influence of regioselective intestinal elimination. Eur J Clin Pharmacol. 2008;64(11):1085–92.
28. Medicines Compendium UK. Detrunorm 15 mg tablets. Summary of product characteristics (online). Available from URL: http://www.medicines.org.uk/emc/medicine/15252. [Accessed 2012 August 6].
29. Medicines and Healthcare products Regulatory Agency. Public assessment report: Mictonorm XL 30 mg modified release capsules, Proprinorm XL 30 mg modified release capsules (online). Available from URL: http://www.mhra.gov.uk/home/groups/I-unit1/documents/websiteresources/con013950.pdf. [Accessed 2012 August 6].
30. Siegmund W, Siegert J, Richter K, et al. Influence of a fat-rich meal on bioavailability of extended-release and immediate-release propiverine. J Clin Pharmacol. 2012;52(5):681–90.
31. Huang M, Tian Y, Zhang Z, et al. Determination of propiverine hydrochloride in human plasma by high performance liquid chromatography-tandem mass spectrometry: application to the pharmacokinetic study of a sustained release formulation. Arzneimittelforschung. 2011;61(9):494–501.
32. Tomalik-Scharte D, Jetter A, Kinzig-Schippers M, et al. Effect of propiverine on cytochrome P450 enzymes: a cocktail interaction study in healthy volunteers. Drug Metab Dispos. 2005;33(12): 1859–66.
33. Siegmund W, Sillen U, Lackgren G, et al. Pharmacokinetics and pharmacodynamics of propiverine in children aged between 5 and 10 years with symptoms of overactive bladder. Clin Pharmacokinet. 2010;49(5):335–42.
34. Schulte-Baukloh H, Mürtz G, Heine G, et al. Urodynamic effects of propiverine in children and adolescents with neurogenic bladder: results of a prospective long-term study. J Pediatr Urol. 2012;8(4):386–92.
35. Mazur D, Wehnert J, Dorschner W, et al. Clinical and urodynamic effects of propiverine in patients suffering from urgency and urge incontinence. A multicentre dose-optimizing study. Scan J Urol Nephrol. 1995;29(3):289–94.
36. Gotoh M, Yokoyama O, Nishizawa O, et al. Propiverine hydrochloride in Japanese patients with overactive bladder: a randomized, double-blind, placebo-controlled trial. Int J Urol. 2011; 18(5):365–73.
37. Dorschner W, Stolzenburg JU, Griebenow R, et al. Efficacy and cardiac safety of propiverine in elderly patients: a double-blind, placebo-controlled clinical study. Eur Urol. 2000;37(6):702–8.
38. Jünemann KP, Hessdorfer E, Unamba-Oparah I, et al. Propiverine hydrochloride immediate and extended release: comparison of efficacy and tolerability in patients with overactive bladder. Urol Int. 2006;77(4):334–9.
39. Lee K-S, Lee HW, Choo M-S, et al. Urinary urgency outcomes after propiverine treatment for an overactive bladder: the 'propiverine study on overactive bladder including urgency data'. BJU Int. 2010;105(11):1565–70.
40. Homma Y, Yamaguchi O, Group IS. A randomized, double-blind, placebo- and propiverine-controlled trial of the novel antimuscarinic agent imidafenacin in Japanese patients with overactive bladder. Int J Urol. 2009;16(5):499–506.
41. Yamaguchi O, Marui E, Kakizaki H, et al. Randomized, double-blind, placebo- and propiverine-controlled trial of the once-daily antimuscarinic agent solifenacin in Japanese patients with overactive bladder. BJU Int. 2007;100(3):579–87.
42. Leng J, Wan B, Du C, et al. Randomized clinical trial evaluating safety and efficacy of propiverine ER 30 mg and tolterodine ER 4 mg in the treatment of overactive bladder (abstract no. 338). International Continence Society Annual Meeting. Beijing; 2012 Oct 15–19.
43. Abrams P, Cardozo L, Chapple C, et al. Comparison of the efficacy, safety, and tolerability of propiverine and oxybutynin for the treatment of overactive bladder syndrome. Int J Urol. 2006;13(6):692–8.
44. Jünemann K-P, Halaska M, Rittstein T, et al. Propiverine versus tolterodine: efficacy and tolerability in patients with overactive bladder. Eur Urol. 2005;48(3):478–82.
45. Madersbacher H, Halaska M, Voigt R, et al. A placebo-controlled, multicentre study comparing the tolerability and efficacy of propiverine and oxybutynin in patients with urgency and urge incontinence. BJU Int. 1999;84(6):646–51.
46. Wada N, Watanabe M, Kita M, et al. Efficacy and safety of propiverine and solifenacin for the treatment of female patients with overactive bladder: a crossover study. LUTS. 2011;3(1): 36–42.
47. Masumori N, Miyamoto S, Tsukamoto T, et al. The efficacy and safety of propiverine hydrochloride in patients with overactive bladder symptoms who poorly responded to previous anticholinergic agents. Adv Urol. 2011. doi:10.1155/2011/714978.
48. Homma Y, Yoshida M, Seki N, et al. Symptom assessment tool for overactive bladder syndrome: overactive bladder symptom score. Urology. 2006;68(2):318–23.
49. Marschall-Kehrel D, Feustel C, Persson de Geeter C, et al. Treatment with propiverine in children suffering from nonneurogenic overactive bladder and urinary incontinence: results of a randomized placebo-controlled phase 3 clinical trial. Eur Urol. 2009;55(3):729–36.
50. Kessler-Zumpe PL, Murgas S, Neumann G, et al. Therapy of overactive bladder with propiverine ER. Results of a non-interventional study with propiverine retard formulation and comparison to clinical studies (in German). Urologe. 2009;48: 1346–51.
51. Alloussi S, Schönberger B, Mürtz G, et al. Treatment of the urge-syndrome with propiverine in therapeutic practice: tolerability and efficacy in 4390 patients (in German). Urologe B. 2000;40: 367–73.
52. Stöhrer M, Madersbacher H, Richter R, et al. 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.
53. Takayasu H, Ueno A, Tsuchida S, et al. Clinical evaluation of propiverine hydrochloride (P4) against pollakisuria and urinary incontinence: a multicenter, placebo-controlled double-blind study (in Japanese). Prog Med. 1990;153:459–71.
54. Stöhrer M, Murtz G, Kramer G, et al. Efficacy and tolerability of propiverine hydrochloride extended release compared to immediate release in patients with neurogenic detrusor overactivity (abstract no. 448). International Continence Society Annual Meeting. San Francisco; 2009 Sep 29 –2009 Oct 3.
55. Stöhrer M, Mürtz G, Kramer G, et al. Propiverine compared to oxybutynin in neurogenic detrusor overactivity: results of a randomized, double-blind, multicenter clinical study. Eur Urol. 2007;51(1):235–42.
56. Bae JH, Kim SO, Yoo ES, et al. Efficacy and safety of low-dose propiverine in patients with lower urinary tract symptoms/benign

prostatic hyperplasia with storage symptoms: a prospective, randomized, single-blinded and multicenter clinical trial. Korean J Urol. 2011;52(4):274–8.
57. Lee KS, Choo MS, Kim DY, et al. Combination treatment with propiverine hydrochloride plus doxazosin controlled release gastrointestinal therapeutic system formulation for overactive bladder and coexisting benign prostatic obstruction: a prospective, randomized, controlled multicenter study. J Urol. 2005; 174(4 Pt 1):1334–8.
58. Nishizawa O, Yamaguchi O, Takeda M, et al. Randomized controlled trial to treat benign prostatic hyperplasia with overactive bladder using an alpha-blocker combined with anticholinergics. LUTS. 2011;3:29–35.
59. Saito H, Yamada T, Oshima H, et al. A comparative study of the efficacy and safety of tamsulosin hydrochloride alone and combination of propiverine hydrochloride and tamsulosin hydrochloride in the benign prostatic hypertrophy with pollakisuria and/or urinary incontinence (in Japanese). Jpn J Urol Surg. 1999; 12:525–36.
60. Seo KI, Hong SZ, Lee JB. The efficacy and safety of combination therapy with alpha-blocker and low-dose propiverine hydrochloride for benign prostatic hyperplasia accompanied by overactive bladder symptoms (in Korean). Korean J Urol. 2009; 50(11):1078–82.
61. Yokoyama T, Uematsu K, Watanabe T, et al. Naftopidil and propiverine hydrochloride for treatment of male lower urinary tract symptoms suggestive of benign prostatic hyperplasia and concomitant overactive bladder: a prospective randomized controlled study. Scand J Urol Nephrol. 2009;43(4):307–14.
62. Matsukawa Y, Hattori R, Mazima T, et al. Is combination therapy with an anticholinergic agent and an alpha1-adrenoceptor antagonist useful as first-line treatment in patients with benign prostatic hyperplasia complicated by overactive bladder? A randomized, prospective, comparative study using a urodynamic study (abstract no. 753). 27th Congress of the European Association of Urology. Paris; 2012 Feb 24–28.
63. Kamimura N, Hatakeyama S, Kudo S, et al. Additional effect of propiverine for naftopidil-resistant nocturia in the patient with benign prostate hypertrophy (in Japanese). Hinyokika Kiyo. 2011;57:71–6.
64. Oelke M, Murgas S, Baumann I, et al. Efficacy of propiverine ER with or without alpha-blockers related to maximum urinary flow rate in adult men with OAB: results of a 12-week, multicenter, non-interventional study. World J Urol. 2011;29(2):217–23.
65. Kim WJ, Lee D-G, Lee SW, et al. Efficacy and safety of propiverine in children with overactive bladder. Korean J Urol. 2012; 53(4):275–9.
66. Alloussi S, Mürtz G, Braun R, et al. Efficacy, tolerability and safety of propiverine hydrochloride in comparison to oxybutynin in children with urge incontinence due to overactive bladder: results of a multicentre observational cohort study. BJU Int. 2010;106(4):550–6.
67. Schulte-Baukloh H, Mürtz G, Henne T, et al. Urodynamic effects of propiverine hydrochloride in children with neurogenic detrusor overactivity: a prospective analysis. BJU Int. 2006;97(2):355–8.
68. Grigoleit U, Mürtz G, Laschke S, et al. Efficacy, tolerability and safety of propiverine hydrochloride in children and adolescents with congenital or traumatic neurogenic detrusor overactivity: a retrospective study. Eur Urol. 2006;49(6):1114–20.
69. Madersbacher H, Mürtz G, Alloussi S, et al. Propiverine vs. oxybutynin for treating neurogenic detrusor overactivity in children and adolescents: results of a multicentre observational cohort study. BJU Int. 2009;103(6):776–81.
70. Apogepha. Mictonetten® 5 mg coated tablets. Product information leaflet (online). Available from URL: http://www.apogepha.de/de/gesundheit/mictonetten.html. [Accessed 2012 Nov 19].
71. Noguchi K, Masuda M, Noguchi S, et al. Longterm administration study of propiverine hydrochloride (BUP-4® tablets) in pollakiuria and urinary incontinence (in Japanese). Hinyokika Kiyo. 1998;44:687–93.
72. Medicines and Healthcare products Regulatory Agency. Public assessment report: Mictonorm XL 45 mg modified release capsules (propiverine hydrochloride) (online). Available from URL: http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con143796.pdf. [Accessed 2012 August 6].
73. Medicines Compendium UK. Detrunorm XL 30 mg modified release capsules. Summary of product characteristics (online). Available from URL: http://www.medicines.org.uk/emc/medicine/18501. [Accessed 2012 Nov 14].
74. Schröder A, Thüroff JW. New strategies for medical management of overactive bladder in children. Curr Opin Urol. 2010;20(4): 313–7.
75. Oelke M, Bachmann A, Descazeaud A, et al. European association of urology. Guidelines of the management of male lower urinary tract symptoms (LUTS), incl. benign prostatic obstruction (BPO). Available from URL: http://www.uroweb.org/gls/pdf/. [Accessed 2012 Sep 6].
76. Chapple CR, Khullar V, Gabriel Z, et al. The effects of antimuscarinic treatments in overactive bladder: an update of a systematic review and meta-analysis. Eur Urol. 2008;54(3):543–62.
77. Asimakopoulos AD, Cerruto MA, Del Popolo G, et al. An overview on mixed action drugs for the treatment of overactive bladder and detrusor overactivity. Urol Int. 2012;89(3):259–69.
78. Blake-James BT, Rashidian A, Ikeda Y, et al. The role of anticholinergics in men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia: a systematic review and meta-analysis. BJU Int. 2006;99(1):85–96.
79. Paquette A, Gou P, Tannenbaum C, et al. Systematic review and meta-analysis: do clinical trials testing antimuscarinic agents for overactive bladder adequately measure central nervous system adverse events? J Am Geriatr Soc. 2011;59(7):1332–9.
80. Uchiyama T, Sakakibara R, Liu Z, et al. The effects of anticholinergic drugs for overactive bladder on cognitive impairment, mental dysfunction and motor dysfunction in patients with neurological disease (abstract no. 245). International Continence Society Annual Meeting. Montreal; 2005 Aug 28–2005 Sep 2.
81. Sakakibara R, Ogata T, Uchiyama T, et al. How to manage overactive bladder in elderly individuals with dementia? A combined use of donepezil, a central acetylcholinesterase inhibitor, and propiverine, a peripheral muscarine receptor antagonist (letter). J Am Geriatr Soc. 2009;57(8):1515–7.
82. Kluge A, Vohs K, Siegert J, et al. Effect of propiverine on psychomotor performance (abstract no. P319). International Continence Society Annual Meeting. Athens; 1996 Aug 27–30.
83. Abrams P, Kelleher CJ, Kerr LA, et al. Overactive bladder significantly affects quality of life. Am J Manag Care. 2000; 6(11 Suppl.):506–14.
84. Cardozo L, Thorpe A, Warner J, et al. The cost-effectiveness of solifenacin vs. fesoterodine, oxybutynin immediate-release, propiverine, tolterodine extended-release and tolterodine immediate-release in the treatment of patients with overactive bladder in the UK National Health Service. BJU Int. 2000;106(4):506–14.