#95

Efficacy and Safety of Doxazosin versus Tamsulosin for the Treatment of Male LUTS – A Network Meta-Analysis

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ABSTRACT

Hypothesis / Aims of Study | Doxazosin and tamsulosin are worldwide available and widely used α_1-adrenoceptor antagonists (α_1-blockers) for the treatment of lower urinary tract symptoms (LUTS) in adult men. Randomized, controlled trials (RCTs) showed that α_1-blockers reduce LUTS, as measured by the International Prostate Symptom Score (IPSS, range 0-35), by 30-40% independent on baseline LUTS severity. The American Urological Association (AUA) guidelines on the "Management of Benign Prostatic Hyperplasia" and the European Association of Urology (EAU) guidelines on the "Treatment on non-neurogenic male LUTS" both state that all α_1-blockers have a similar clinical effectiveness but differ in tolerability when used in appropriate doses [1, 2]. However, these statements are based on indirect comparisons and only few direct comparisons between different α_1-blockers. To test this hypothesis, we compared the efficacy and safety of different doses and formulations of doxazosin (immediate release 2 mg, 4 mg or 8 mg and gastrointestinal therapeutic system [GITS] 4 mg or 8 mg) versus tamsulosin (modified release 0.2 mg, 0.4 mg, 0.8 mg or oral controlled absorption System [OCAS] 0.4 mg) in a network meta-analysis of clinical trial data.

Study Design, Materials and Methods | The PubMed, EMBASE and Cochrane databases were systematically searched to identify randomized, controlled clinical trials with doxazosin or tamsulosin. Bayesian random effects models estimated efficacy and safety outcomes, including total IPSS (IPSS-T), IPSS-quality of life (QoL) and any adverse events (AEs). Comprehensive assessments, including tests for heterogeneity, similarity, and consistency ensured unbiased and accurate estimates.

Results | In total, 1,518 abstracts on doxazosin and/or tamsulosin were identified and reviewed of which 40 trials with 12,201 patients were included in our analyses. Improvement of IPSS-T and QoL (mean [95% credible interval, CrI]) were largest for doxazosin GITS 4 mg (IPSS-T: -10.08 points [-12.00, -8.21]; QoL: (-1.82 points [-2.25, -1.38]). Mean probability of any AE ranged from 0.15 to 0.40.

Interpretation of Results |Our findings suggest for the first time that improvements in IPSS-T and QoL were significantly greater and the adverse event rates were similar for doxazosin GITS 4 mg compared with most tamsulosin doses and formulations.

Concluding Message | Contrary to the AUA and EAU guidelines statements, we found significantly greater clinical effectiveness in terms of total IPSS decrease and QoL increase for doxazosin GITS 4 mg compared with tamsulosin but a similar frequency of AEs.

METHODS

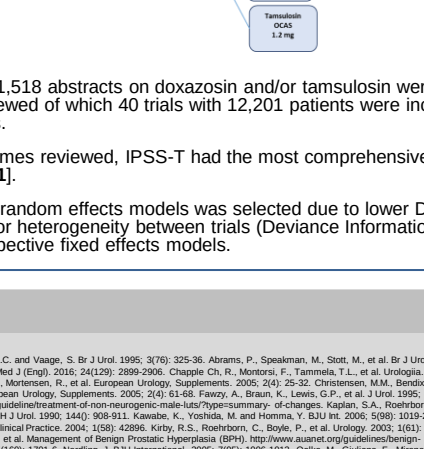
The PubMed, EMBASE and Cochrane Database of Systematic Reviews databases were systematically searched to identify randomized, controlled clinical trials with doxazosin or tamsulosin. Bayesian models estimated efficacy and tolerability outcomes, including total IPSS (IPSS-T), IPSS-quality of life (QoL) and any adverse events (AEs). Comprehensive assessments, including tests for heterogeneity, similarity, and consistency ensured unbiased and accurate estimates.

Table 1. Search Terms Strings

BPH
("benign prostatic hyperplasia" OR "prostatic hyperplasia" OR "BPH" OR "lower urinary tract symptom" OR "lower urinary tract symptoms" OR "LUTS" OR "bladder outlet obstruction" OR "benign prostatic obstruction") AND
Doxazosin
("doxazosin" OR "doxazosin mesylate" OR "cardura" OR "carduran" OR "cardura XL" OR "cascor") AND
Tamsulosin
("tamsulosin" OR "flomax" OR "tamsulosin hydrochloride" OR "flomaxtra" OR "harnal D" OR "harnal" OR "omnic" OR "OCAS")

- Abstracts published prior to Dec 2016 were included; randomized clinical trials including a head-to head comparison between doxazosin and/or tamsulosin and/or placebo and reporting one or more efficacy or tolerability end points were included.
- Studies published only in abstract/conference presentation form, studies with non-human subjects (pre-clinical studies), and studies with indications other than LUTS/BPH were excluded.
- Two reviewers independently screened each title and abstract to determine relevant articles for full-text review, with any discrepancies resolved with a third reviewer.

Figure 1. Doxazosin versus Tamsulosin for the Treatment of Male LUTS NMA Network (IPSS-T)



- In total, 1,518 abstracts on doxazosin and/or tamsulosin were identified and reviewed of which 40 trials with 12,201 patients were included in our analyses.
- Of outcomes reviewed, IPSS-T had the most comprehensive network [**Figure 1**].
- Baysian random effects models was selected due to lower DIC and control for heterogeneity between trials (Deviance Information Criterion) than respective fixed effects models.

RESULTS

- Baseline patient characteristics were not consistently reported by all 40 studies
- For studies reporting baseline characteristics (**Table 2**): Mean age ranged from 53.9 to 74.4 yrs; BPH duration: 1.6 to 7.6 yrs; Prostate volume: 32.9 to 59.9 mL; IPSS-T: 13.3 to 21.8; Q_{max}: 7.4 to 12.9 mL/s

Table 2. Selected Studies and Reported Baseline Characteristics

Author, Yr	Study Characteristics		Patient characteristics				
	Countries	Pop	Mean Age (yrs)	BPH duration (yrs)	Prostate volume (mL)	IPSS-T	Qmax (mL/sec)
Abrams, 1995	EU	ITT	63.8	-	-	-	10.6
Abrams, 1997	UK	ITT	65	-	-	-	9.9
Andersen, 2000	EU	ITT	65.2	3.6	-	17.8	10.1
Cai, 2016	China	-	69.5	7.6	41.8	18.3	12
Chapple, 2012	EU	ITT	65.9	-	-	19.1	10.4
Chapple, 1994	UK	-	67	3.5	-	-	9.1
Christensen, 1993	Denmark	-	67.4	2.4	-	-	7.6
Fawzy, 1995	US	-	61.9	5.3	-	-	9.8
Kaplan, 2008	US	ITT	61.8	5.3	33.9	19.9	12.9
Kawabe, 2006	Japan	-	65.3	-	35.6	17	9.8
Lepor, 1998	US	ITT	-	-	-	-	9.6
Narayan, 1998	US	ITT	58	-	-	-	-
Ozbey, 1999	Turkey	-	-	-	-	-	10.5
Pompeo, 2006	Brazil	ITT	62.2	-	-	21.4	11.5
Yokoyama, 2013	APAC	ITT	63.1	3.7	34.8	16.8	12.4
Akan, 1998	Turkey	-	62.1	-	-	18	10.9
Chapple, 2005	EU	ITT	64.7	-	44	18.5	9.7
Chapple, 2005	EU	ITT	65.1	-	41.6	17.9	9.7
Chung, 2011	Korea	ITT	61.6	-	34.5	19.3	-
Djavan, 2005	EU	ITT	67.2	-	56.8	18.2	9.6
Gillenwater, 1995	US	-	64.1	5.2	-	-	-
Kaplan, 2006	US	ITT	61.8	5.3	-	19.9	12.9
Kim, 2011	Korea	ITT	61.6	-	-	17.3	11.2
Kirby 2003 & 2004	-	ITT	65	-	-	18.5	-
Mohanty, 2003	India	-	62	1.8	-	19	11.1
Nordling, 2005	EU	ITT	64.5	4	-	17.6	9.1
Oelke, 2012	Global	-	63.6	-	-	17.1	9.9
Raharjdo, 2006	Indonesia	ITT	64.7	-	32.9	18.7	10.3
Singh, 2012	India	ITT	-	-	-	20	-
Van Kerrebroeck, 2013	EU	FAS	65.4	-	36.5	18.7	8.9
Van Kerrebroeck, 2013	EU	-	65.4	-	41.9	18.5	-
Xue, 2007	China	ITT	66.1	5.1	39.4	21.8	10.8
Zhang, 2011	China	-	68.6	1.7	41.8	19	9.4
Kirby, 2003	US	ITT	63.5	1.63		17.2	10.45
Lepor, 1998 (LT)	US	ITT	-	-	-	-	9.6
McConnell, 2003	US	ITT	62.6	-	36.3	16.9	10.5
Prieto, 2008	US	-	74.4	-	59.9	-	-
Shelbaia, 2013	Egypt	-	53.9	-	-	13.3	-
Kawabe, 1990	-	-	68	-	-	-	-
Rollema, 1991	Netherlands	-	-	-	-	-	7.4

- Improvement of IPSS-T and QoL (mean [95% credible interval, CrI]) were largest for doxazosin GITS 4 mg (IPSS-T: -10.08 points [-12.00, -8.21]; QoL: (-1.82 points [-2.25, -1.38]) [**Table 3**]
- Mean probability of any AE ranged from 0.15 to 0.40

Table 3. Mean differences in IPSS-T and QoL as well as mean odds ratios of any AE for different doxazosin versus tamsulosin doses/formulations [mean (95% CrI)]

	DOXAZOSIN				
TAMSULOSIN	**2 mg**	**4 mg**	**8 mg**	**GITS 4 mg**	**GITS 8 mg**
IPSS-T [a]					
0.2 mg	-2.01 (-5.67,1.63)	0.76 (-3.60,5.12)	0.11 (-2.29,2.48)	**2.88 (1.18,4.63)***	-0.21 (-3.62,3.16)
0.4 mg	-2.98 (-6.97,0.95)	-0.21 (-4.50,4.03)	-0.86 (-3.11,1.32)	**1.91 (0.02,3.82)***	-1.18 (-4.48,2.10)
0.8 mg	-3.38 (-7.63,0.88)	-0.61 (-5.13,3.89)	-1.26 (-3.93,1.39)	1.52 (-0.97,4.02)	-1.57 (-5.20,1.99)
OCAS 0.4 mg	-1.63 (-5.77,2.51)	1.14 (-3.27,5.53)	0.49 (-2.01,2.94)	**3.26 (0.89,5.68)***	0.17 (-3.29,3.63)
IPSS-QoL [a]					
0.2 mg			0.17 (-0.38,0.71)	**0.51 (0.13,0.88)***	0.07 (-0.48,0.61)
0.4 mg			0.22 (-0.34,0.78)	**0.56 (0.04,1.08)***	0.12 (-0.44,0.68)
0.8 mg					
OCAS 0.4 mg			0.16 (-0.39,0.70)	**0.51 (0.00,1.00)***	0.06 (-0.49,0.60)
Any AE [b]					
0.2 mg		1.44 (0.69,2.70)	**0.40 (0.15,0.87)***	0.79 (0.46,1.29)	
0.4 mg		1.76 (0.89,3.20)	0.49 (0.19,1.04)	0.98 (0.59,1.52)	
0.8 mg		1.49 (0.72,2.77)	**0.41 (0.16,0.89)***	0.82 (0.47,1.35)	
OCAS 0.4 mg		1.85 (0.91,3.37)	0.51 (0.20,1.09)	1.03 (0.60,1.65)	

Blank cells: data not available. Current table simplifies to display available dosages only.

[a] Positive values: higher reduction in IPSS scores for doxazosin than tamsulosin
[b] Values<1: lower odds of any AE for doxazosin than tamsulosin
* Statistically significant based on 95% CrI

CONCLUSIONS

This NMA, inclusive of 40 clinical trials with >12,000 patients, found that improvements in IPSS-T and QoL were significantly greater and the adverse event rates were similar for doxazosin GITS 4 mg compared with most tamsulosin doses and formulations. Reflectively updates to AUA and EAU guidelines should consider integration of these clinical findings.

DISCLOSURES

This NMA was sponsored by Pfizer. M Oelke has no financial relationship with Pfizer Inc. to the present study. Patel D and Chopra I were employees of Pharmerit, who were paid consultants to Pfizer in connection with the study and development of this poster. Tang W and Hassan T are employees of Pfizer.

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