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PERCEIVED RANDOMIZATION AFFECTS OBJECTIVE, SUBJECTIVE, AND QUALITY OF LIFE OUTCOMES IN URGE INCONTINENCE TREATMENT

Aims of Study

Drug therapy trials for urge urinary incontinence (UI) always have shown some placebo effect. Previous work demonstrated that in a randomized controlled trial (RCT), blinded patients (pts) with urge UI often could identify whether they had taken immediate-release oxybutynin (96% correct) or placebo (61% correct) ($p<.001$) [1]. More strikingly, subjects who thought they were on active drug had significantly better percent decrease in urinary incontinence compared with subjects who thought they had taken placebo (80-83% vs. 1.1-7.2%, $p=.01$), regardless of their actual randomization [1]. However, this trial was small and used an agent with high rates of anticholinergic side effects. Therefore, we investigated whether a larger trial of an agent with less anticholinergic side effects would yield similar results

Methods

Data were obtained from an 8-week, multicenter double-blind RCT of extended-release tolterodine 4 mg/day (T, n=536) vs placebo (P, n=263) in women with mixed urinary incontinence who answered the question about treatment assignment. Capsules for drug and placebo were physically identical, and subjects were aware of the 2:1 T:P randomization. Incontinence outcomes were based 7-day bladder diaries (urge UI episodes), subjective outcomes, and a disease-specific quality of life measure (King's Health Questionnaire [KHQ]). At trial completion subjects were asked which agent they thought they had been given. Chi-square and Wilcoxon rank sum tests were used for analyses.

Results

Data are presented from the intention-to-treat analysis. 58% of subjects correctly identified that they were on active drug, 37% correctly identified that they were on placebo, and 27% said they did not know. Overall, 51% of subjects correctly identified their randomization. Subjects randomized to tolterodine (RT) correctly identified their randomization more often than subjects given placebo (RP) (58% vs 37%, $p<0.01$). All subjects who thought they were on active drug (PT) had significantly better objective and subjective outcomes than subjects who thought they were on placebo (PP). However, efficacy outcomes were similar for all subjects who thought they had received active therapy, irrespective of actual randomization (Table).

Table. Urge UI outcomes, by randomization and subject perception of drug assignment.

		Randomization	
Perception	Measure*	Tolterodine (RT)	Placebo (RP)
Tolterodine (PT)	Median ↓urge incontinence	-88.9%	-80%
N=405	↓urge UI episodes/24 hr	-2.3	-1.7
	Improved bladder condition	76.5%	75.7%
	Subjective response to Rx	97.4%	93.6%
	Significant improvement in KHQ	All domains	Emotions
Placebo (PP)	Median ↓urge incontinence	-30.7%	-19.9%
N=177	↓urge UI episodes/24 hr	-0.8	-0.1
	Improved bladder condition	29.6%	17.7%
	Subjective response to Rx	11.1%	10.4%
	Significant improvement in KHQ	All domains	Symptom severity, sleep/energy
Don't know			
N=217			

*excludes "Don't know" subjects

Conclusions 1) We confirm that RCTs of antimuscarinic drugs for urge incontinence must be reinterpreted because half of subjects are not blinded—*even with agents known to have less side anticholinergic effects*. 2) Drug therapy of urge incontinence has a powerful placebo effect involving objective, subjective, and quality of life outcomes, which may obscure actual drug efficacy. 3) New trial designs that can counter or control for patient expectations of improvement, and which explore confounding of patient outcomes by positive or negative impact of anticholinergic side effects, are needed to better understand the role of antimuscarinic agents in treating urge incontinence.

Reference

1. DuBeau CE, Miller KL, Bergmann M, Resnick NM. Urge incontinence outcomes in RCTs depend on assumed and not actual drug assignment. International Continence Society 30th Annual Meeting, Tampere, Finland, August, 2000.