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α-Blocker Use Is Associated With Decreased Risk of Sexual Dysfunction

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Abstract

OBJECTIVES—To examine the association between *α*-blocker use and sexual dysfunction among men participating in a population-based cohort of men residing in Olmsted County, MN. Lower urinary tract symptoms (LUTS) in men have previously been associated with sexual dysfunction. The use of *α*-adrenergic receptor blocking agents results in an improvement in LUTS for many men. If sexual dysfunction and LUTS share a common etiology, *α*-blocker use might also be associated with a decreased risk of sexual dysfunction.

METHODS—White men, aged 40-79 years, were randomly selected in 1990 and assessed for *α*-blocker use and LUTS severity. Sexual function was assessed using the Brief Male Sexual Function Inventory. Men who used *α*-blockers before any sexual dysfunction were considered "exposed." Hazard ratios and 95% confidence intervals were estimated separately for each sexual function domain using Cox proportional hazard models.

RESULTS—Of the 1724 men with a regular sexual partner included in the present study (mean age 57.74 years), 263 (15.3%) reported *α*-blocker use. *α*-Blocker use was associated with a decreased risk of sexual dysfunction across all domains for men ≥50 years old (age-adjusted hazard ratio 0.53-0.69). A decreased risk of erectile dysfunction and low libido remained significant only among those using *α*-blockers who also experienced an improvement in LUTS (*P* = .01).

CONCLUSIONS—The use of *α*-blockers for LUTS was associated with a decreased risk of sexual dysfunction. Improvement in sexual function correlated with the improvement in LUTS more strongly among those using *α*-blockers.

Sexual dysfunction is a common phenomenon in aging men. It progressively increases with age and is associated with a poor quality of life.[1,2] Sexual function consists of a number of domains. The major domains are erectile function, sexual drive, and ejaculatory function, and any or all of these can be affected and cause sexual dysfunction. Lower urinary tract symptoms (LUTS) are also a frequent occurrence in aging men, and a number of publications have evaluated the association between these 2 conditions.[1-3]

Most of the current reports have examined the frequency of simultaneous occurrence of LUTS and sexual dysfunction and the relative risk conferred by the presence of 1 on the

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occurrence of the other.[1,2] For example, the Multinational Survey of the Aging Male is 1 of the largest population-based studies, specifically designed to evaluate the association between LUTS and sexual dysfunction in aging men.[2] Its results, based on a survey completed by 12 815 men from the United States and 6 European countries, suggested that the presence of LUTS is the strongest predictor for the occurrence of erectile dysfunction, even greater than diabetes and cardiac disease.

Apart from epidemiologic data showing an association between LUTS and sexual dysfunction, a number of theories support a common pathophysiology for these 2 conditions.[3] Potential mechanisms include a deficiency of nitric oxide, autonomic hyperactivity, increased Rho kinase and endothelin activity, and pelvic atherosclerosis. The results of clinical trials evaluating common therapeutic strategies have further strengthened the likelihood of a common pathophysiology. The ALFuzosin-ONcE Daily study group noted improvement in sexual function in men with concomitant erectile dysfunction and/or ejaculatory dysfunction and LUTS after 1 year of therapy with alfuzosin.[4]

These studies support an association between LUTS and sexual dysfunction. A logical corollary of these studies would be the assumption that therapy for LUTS might delay or prevent the occurrence of sexual dysfunction in men in whom it is not already present at baseline. Therefore, we examined the association between the use of α-blockers and the occurrence of sexual dysfunction among men participating in the longitudinal, population-based Olmsted County Study of Urinary Symptoms and Health Status among Men.

MATERIAL AND METHODS

Study Population

The details related to the study population have been previously published.[5,6] In brief, a cohort of white men aged 40-79 years was randomly selected from the 1990 Olmsted County, MN population. Men who had a history of prostate or bladder surgery, urethral surgery or stricture, or medical or other neurologic conditions that could affect normal urinary function were excluded. After excluding the men with these conditions, 3874 men were asked to participate in the study, and 2115 (55%) agreed and completed a self-administered questionnaire.

The cohort was actively followed up on a biennial basis for 14 years using a protocol similar to that at baseline. During the second and third round of visits, men who did not participate in the follow-up were replaced by men randomly selected from the community, after screening for the exclusion criteria used at baseline (n = 332).

The Mayo Foundation and Olmsted Medical Center institutional review boards approved all study procedures.

Assessment of α-Blocker Use

The study participants were asked (by structured interview) to report all prescribed and over-the-counter medications taken daily at the initial study visit. The dosage, unit of administration, starting date, and directions for use of each medication were recorded when such information was available. When possible, the medication information was recorded directly from the bottle label. The use of all medication has been assessed by questionnaire biennially since the fifth follow-up round (2000). Additionally, beginning in 1998 and biennially thereafter, questions about specific benign prostatic hyperplasia (BPH) medical treatments, including α-blockers and finasteride, were added to the questionnaire. Participants who reported daily α-blocker use before an indication of sexual dysfunction were considered “exposed.”

Sexual Dysfunction Assessment

The Brief Male Sexual Function Inventory was incorporated into the follow-up questionnaire in 1996 and biennially thereafter.[7] This previously validated questionnaire consists of 11 items related to 5 sexual function domains: sexual drive (2 questions), erectile function (3 questions), ejaculatory function (2 questions), sexual problem assessment (3 questions), and overall sexual satisfaction (1 question). All questions are scored on a scale of 0-4, with domain scores equaling the sum of the individual questions in each domain. The domain scores range from 0 to 12 for erectile function and sexual problem assessment, 0 to 8 for sexual drive and ejaculatory function, and 0 to 4 for overall sexual satisfaction. For categorical analysis, the following cutpoints were used to define sexual dysfunction: low libido if the sexual drive domain score was ≤2, erectile dysfunction if the erectile function domain score was ≤3, ejaculatory dysfunction if the ejaculatory function domain score was ≤2, sexual problems if the problem assessment domain score was ≤3, and low sexual satisfaction if the sexual satisfaction domain score was ≤1.[8] Sexual function data were available for 1904, 1540, 1573, 1388, and 1137 men from the fourth to eighth rounds of follow-up, respectively.

LUTS Assessment

At each round, the participants completed a self-administered questionnaire regarding LUTS severity, with questions similar to the American Urologic Association Symptom Index.[9] The American Urologic Association Symptom Index has been previously validated for assessing urologic symptom severity and has excellent test-retest reliability.

Statistical Analysis

The men were followed up from the fourth round of the study (1996) until the occurrence of a sexual dysfunction event (as described in the previous section) or the last study visit. Previous work has shown that self-reported sexual function can be heavily influenced by the availability of a regular sexual partner.[7] Therefore, only those men with a regular sexual partner were included in the analyses. The observations for men who began taking a phosphodiesterase-5 inhibitor or finasteride or who underwent surgery for BPH, who died, or who were lost to follow-up were censored at the date of the event (n = 300 men with observations censored). Men with treatment before the initial sexual function assessment were excluded from the analyses.

Bivariate and age-adjusted hazard ratios and 95% confidence intervals were estimated separately for each sexual function domain using Cox proportional hazard models. The proportionality assumption was checked with the use of scaled Schoenfeld residuals and visually using log-log plots.[10]

The changes in the sexual function domain score and symptom score were assessed from the score before α-blocker use to the score at the last study visit for those using α-blockers. For those not using α-blockers, the changes in sexual function domain score and symptom score were assessed from the first study visit assessing sexual function to the last study visit. For the present study, an improvement in LUTS was defined as a decline of ’2 points in the symptom score. Age-adjusted Spearman correlations and hazard ratios were used to assess the associations among changes in the American Urologic Association Symptom Index scores, changes in sexual function, and α-blocker use.

RESULTS

A total of 1724 men participated in the study. The mean age of this cohort in 1996 was 57.7 years. Of these men, 263 (15.3%) reported use of α-blocker drugs. The first α-blockers

reported for use by these men were doxazosin (n = 93; 35%), prazosin (n = 4; 2%), terazosin (n = 87; 33%), and tamsulosin (n = 79; 30%). The increase in α-blocker use with increasing age was significant (Table 1). Additionally, the incidence of hypertension and coronary heart disease was greater among those using α-blockers and might have been one of the reasons for the drug prescription. The presence of sexual dysfunction was similar in both those using and those not using α-blockers at baseline, with low sexual satisfaction the most common problem (Table 1).

The association between α-blocker use and the risk of sexual dysfunction is presented in Table 2. The use of α-blockers was associated with a decrease in sexual dysfunction across all sexual function domains. Although this decrease was not apparent in the unadjusted hazard ratios, it was evident for each of the 5 domains after the ratios had been adjusted for age. The association was similar in each of the 5 domains.

α-Blockers are frequently prescribed to improve bothersome LUTS. To evaluate the effect of LUTS on sexual dysfunction, we examined the correlations between the changes in symptom scores and those in sexual function after adjusting for age. The changes in symptom score correlated marginally with the changes in sexual function in each of the 5 domains (Table 3). The negative correlation indicated that an improvement in sexual function (an increase in score) correlated with an improvement (decline) in symptom score. These correlations were then examined separately for those taking and not taking α-blockers. The correlations were again marginal for men not using α-blockers but were stronger for those who did take these drugs. The correlations between improvement in LUTS and improvement in erectile function and overall sexual satisfaction increased from −0.07 to −0.22 and −0.08 to −0.20, respectively, when the subset was confined to those taking α-blockers (Table 3).

Because α-blocker use, LUTS, and sexual dysfunction seemed to be interrelated, we evaluated these associations further (Table 4). Using men who did not use an α-blocker and reported no improvement in LUTS as the reference group, we found that those who used α-blockers and experienced an improvement in LUTS also tended to have decreased sexual problems (hazard ratio 0.38-0.78) compared with the men who did not use α-blockers and reported no improvement in LUTS (Table 4). Additionally, although not statistically significant, a lower risk of sexual dysfunction (hazard ratio 0.70-0.85) was associated with α-blocker use even without an improvement in LUTS (Table 4). All hazard ratios were adjusted for age and baseline comorbidities, including diabetes, hypertension, coronary heart disease, and mental health score.

COMMENT

Our findings suggest that for men ≥50 years old, α-blocker use is associated with a reduced risk of the subsequent development of sexual dysfunction. We found this association in each of the 5 domains of sexual function, including erectile function, ejaculatory function, sexual drive, sexual problem assessment, and overall sexual satisfaction. We also found that men with improvement in LUTS after α-blocker treatment were less likely to develop sexual dysfunction compared with those who did not use α-blockers and did not show an improvement in LUTS.

The causal relationship between LUTS and sexual dysfunction has not been clearly defined.[11] Sexual dysfunction and LUTS are both symptom complexes rather than individual disease entities. Both conditions are multifactorial, and the association between them might originate from both common etiologic factors and, at least in a subset of cases, a common pathophysiology. It is, therefore, plausible that common therapeutic strategies might result

in a benefit for both conditions only in the subgroup of patients in whom both conditions have the same pathophysiology. This could also explain the lack of a consistent association, proven temporal relationship, and consistent treatment effect, which would be necessary to prove "causality" based on Hill's criteria.[11] Among men with LUTS, this probably includes a subgroup whose symptoms are due to BPH/bladder outlet obstruction (BOO).

An improvement in sexual function could result from a direct effect of α-blockers on cavernosal smooth muscle or indirectly by an improvement in LUTS. Goldstein[12] previously demonstrated that oral administration of the α-blocker phentolamine as monotherapy for erectile dysfunction resulted in an improvement in function in ≤53% of men. Although our results were not statistically significant, we found a trend that suggested even men who did not have an improvement in LUTS tended to have a decreased risk of sexual dysfunction across all domains if they had received α-blocker therapy, suggesting that an improvement in LUTS does not fully explain the decreased risk of dysfunction seen for those taking α-blockers. This might be a manifestation of a direct effect of α-blockers on sexual function, independent of their effect on LUTS; however, we lacked the power to stringently test this hypothesis.

An improvement in BPH/BOO-induced LUTS in itself might result in an improvement in sexual function. This could be related to the ultrastructural changes in the corpus cavernosum seen in men with BOO. Demir et al.[13] determined the contractile and relaxant properties of the human corpus cavernosum smooth muscles in men with BOO. They found greater contractility with phenylephrine and greater relaxation with doxazosin in men with severe erectile dysfunction and BOO than in those who did not have obstruction. This was further supported by studies that showed that even surgical relief of BPH can be associated with improvement in sexual function.[14] Our results showed a stronger decreased risk of sexual dysfunction for men using α-blockers than in those with improved LUTS without the use of α-blockers, suggesting that although improvement in LUTS itself contributes to the improvement in sexual function, a direct effect from α-blockers might also exist.

When we consider a common pathophysiologic basis for both LUTS and sexual dysfunction, it would be expected that improvement in 1 would be associated with improvement in the other.[11] van Moorselaar et al.[4] evaluated the effect of the α-blocker alfuzosin on sexual function in 2434 men with LUTS. At baseline, the men with the greatest severity of LUTS had the greatest impairment in sexual function. After therapy, significant improvement from baseline was seen in erectile function, ejaculatory function, and ejaculatory pain. They also noted that the degree of improvement in sexual function correlated with the magnitude of improvement in LUTS and bother. Similar results have been reported with other α-blocking agents routinely used in the management of LUTS due to BPH/BOO.[15,16] Kirby et al.[15] reported a retrospective, multicenter analysis of the effects of doxazosin on the sexual health of men aged 50-80 years with concomitant BPH and erectile dysfunction. Of the 237 men who had erectile dysfunction at baseline, 13%-41% had a clinically and statistically significant improvement in each of the 5 domains of the International Index of Erectile Function. In our study, men with improvement in LUTS from α-blocker therapy had the greatest associated sexual function improvement. This suggests a possible synergism between the direct effect of α-blockers and improvement in LUTS due to BOO on sexual function.

It is likely that the improvement in LUTS that did not originate from BOO will not result in significant improvement in sexual function. Men who did not use α-blockers had marginal correlations between improvements in LUTS and improvements in all sexual function domains. Additionally, of those who did not use α-blockers, the men who had improved LUTS had virtually the same sexual function levels as those who did not have improved

LUTS. An improvement in LUTS without α-blockers or surgery suggests that the etiology of LUTS in these men was probably not BPH/BOO, which is unlikely to resolve spontaneously. Thus, an improvement in LUTS would not be expected to be associated with an improvement in sexual function.

One limitation of our study was that the use of α-blockers was derived from patient self-report, and we did not consider the duration of use, dosage, or type of α-blocker in the analysis. Because a relatively small number of men used α-blockers, we also lacked the power to conduct subanalyses to determine whether different types of α-blockers might have exerted different effects. It is also possible that some patients discontinued use during the study period. The indication for the use of α-blockers was also not defined and might not always have been LUTS. This could have resulted in variability in the dose prescribed, particularly when it was used for hypertension. Additionally, our study population consisted only of white men >40 years old, and our results might not be generalizable to other racially diverse populations or age groups. However, we currently have no reason to believe that the biologic mechanisms leading to LUTS and sexual dysfunction differ among racial and ethnic groups.

CONCLUSIONS

The use of α-blockers for LUTS by men ≥50 years old was associated with a decreased risk of sexual dysfunction. This decrease was seen uniformly in all domains of sexual function. The improvement in sexual function correlated with improvement in LUTS among men using α-blockers, because men with an improvement in symptom score had the strongest associated improvement in sexual function.

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Table 1

Patient characteristics*

Characteristic	α-Blocker Use	No α-Blocker Use	*P* Value	
			χ^2	Age-adjusted χ^2
Age at 1/1/1996 (y)			<.0001	
40-49	43 (16.35)	475 (32.51)		
50-59	67 (25.48)	500 (34.22)		
60-69	92 (34.98)	304 (20.81)		
≥70	61 (23.19)	182 (12.46)		
>1 Physician visit/y at baseline	125 (48.08)	621 (42.83)	.12	.17
Baseline diabetes	11 (4.18)	50 (3.42)	.54	.81
Baseline hypertension	60 (22.99)	259 (17.80)	.047	.52
Coronary heart disease	64 (24.33)	277 (18.96)	.04	.74
Mental health score <25th percentile	45 (20.55)	246 (22.45)	.54	.77
Erectile function domain score ≤3	40 (21.28)	367 (26.35)	.14	.001
Sexual drive domain score ≤2	54 (29.19)	448 (31.84)	.47	.01
Ejaculatory function domain score ≤2	36 (17.73)	269 (19.44)	.57	.01
Sexual problem assessment domain score ≤3	30 (14.49)	219 (15.86)	.61	.07
Sexual satisfaction domain score ≤1	48 (25.53)	457 (32.62)	.05	.01

Data presented as numbers of patients, with percentages in parentheses.

*Totals vary for each variable because of missing data and censoring; percentages calculated using nonmissing data.

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Table 2

Associations between α-blocker use and risk of sexual dysfunction

	No α-Blocker Use		α-Blocker Use			
Sexual Function Outcome Score	**Events (n)**	**Person-Years**	**Events (n)**	**Person-Years**	**Unadjusted HR (95% CI; *P* Value)**	**Age-adjusted HR (95% CI; *P* Value)**
Erectile function domain ≤3	367	7825	40	1039	0.85 (0.61-1.17; .31)	0.53 (0.38-0.74; <.01)
Sexual drive domain ≤2	448	7620	54	996	0.95 (0.72-1.26; .72)	0.61 (0.46-0.81; <.01)
Ejaculatory function domain ≤2	269	8304	36	1104	1.04 (0.74-1.48; .81)	0.62 (0.44-0.89; .01)
Sexual problem assessment domain ≤3	219	8311	30	1151	1.01 (0.69-1.48; .97)	0.69 (0.47-1.02; .06)
Sexual satisfaction domain ≤1	457	7357	48	988	0.80 (0.59-1.08; .14)	0.66 (0.49-0.89; .01)

HR hazard ratio; CI confidence interval.

Table 3

Spearman correlations between changes in symptom score and sexual function, adjusted for age

	Overall		No α-Blocker Use		α-Blocker Use	
Sexual Function Domain	**Correlation**	***P* Value**	**Correlation**	***P* Value**	**Correlation**	***P* Value**
Change in erectile function	−0.07	.01	−0.06	.04	−0.22	.05
Change in sexual drive	−0.07	.02	−0.06	.04	−0.13	.27
Change in ejaculatory function	−0.07	.02	−0.07	.03	−0.10	.37
Change in problem assessment	−0.11	<.0001	−0.11	<.001	−0.15	.18
Change in sexual satisfaction	−0.08	.01	−0.07	.03	−0.20	.09

Table 4

Associations between sexual function domains and interaction of α-blocker use and LUTS improvement adjusted for age and comorbidities*

	Score				
α-Blocker Use; LUTS Improvement	**Erectile Function Domain ≤3**	**Sexual Drive Domain ≤2**	**Ejaculatory Function Domain ≤2**	**Sexual Problem Assessment Domain ≤3**	**Sexual Satisfaction Domain ≤1**
No; no	Reference	Reference	Reference	Reference	Reference
No; yes	0.99 (0.76-1.27; .91)	0.93 (0.73-1.18; .55)	0.92 (0.68-1.24; .56)	1.09 (0.79-1.51; .59)	1.12 (0.89-1.41; .32)
Yes; no	0.70 (0.47-1.06; .10)	0.85 (0.60-1.20; .36)	0.82 (0.53-1.28; .38)	0.85 (0.52-1.39; .51)	0.83 (0.58-1.20; .33)
Yes; yes	0.38 (0.20-0.75; .01)	0.48 (0.27-0.86; .01)	0.59 (0.31-1.12; .10)	0.78 (0.38-1.59; .49)	0.66 (0.35-1.23; .19)
Interaction term *P*-value (α-blocker use × LUTS improvement)	.15	.16	.54	.69	.35

LUTS = lower urinary tract symptoms.

Data presented as hazard ratio, with 95% confidence intervals and *P* value in parentheses.

*Diabetes, hypertension, coronary heart disease, and/or mental health score 25th percentile.

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