

TITLE PAGE

Efficacy of Non-Drug Lifestyle Measures for the Treatment of Nocturia

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Running head:

Lifestyle modifications for nocturia

Keywords:

Lifestyle modification

Nocturia

Quality of life

Word count of text: 2123

Word count of the abstract: 249

33 **ABSTRACT**

34

35 **Purpose:** Nocturia has a major impact on quality of life and affects
36 numerous aspects of health. Lifestyle modifications are expected to
37 be helpful in improving nocturia; however, the efficacy of this
38 strategy has not been established. The aim of this study is to test
39 the efficacy of non-drug lifestyle measures as a first step to treat
40 nocturia and to find factors predictive of the efficacy of the
41 intervention.

42 **Materials and Methods:** We conducted a prospective evaluation on 56
43 patients treated at three hospitals between 2005 and 2009 for
44 symptomatic nocturia. The patients were advised to modify their
45 lifestyle in order to improve nocturia. Lifestyle modifications
46 consisted of four directives - restriction of fluid intake, refraining
47 from excess hours in bed, moderate daily exercise and keeping warm
48 in bed. The frequency volume chart, International Prostate Symptom
49 Score and Pittsburgh Sleep Quality Index before and 4 weeks after
50 the intervention were used to evaluate the efficacy of the therapy.

51 **Results:** The mean number of nocturnal voids and the nocturnal urine
52 volume significantly decreased from 3.6 to 2.7 ($p < 0.0001$) and from
53 923 ml to 768 ml ($p = 0.0005$), respectively. Of the 56 patients, 26
54 (53.1%) showed an improvement of more than one episode. This treatment
55 was significantly more effective in patients with a larger amount

56 of 24 h urine production.

57 **Conclusions:** Non-drug lifestyle measures were effective in reducing
58 the number of nocturia episodes and improving patients' quality of
59 life. Patients with polyuria showed a better response to the treatment.

60 **Introduction**

61

62 Nocturia has a major impact on quality of life, affecting numerous
63 aspects of health, contributing to fatigue, memory deficits,
64 depression, increased risk of heart disease, and gastrointestinal
65 disorders.¹⁻⁴ Nocturnal or global polyuria, reduced nocturnal bladder
66 capacity and sleep disturbance are the possible causes of nocturia.^{5,6}
67 Medical therapy with anticholinergic agents, desmopressin and time
68 release diuretics is often considered as first line treatment
69 depending on the diagnosis and underlying cause; however, medication
70 has a potential risk of adverse events and would also cause problems
71 with national medical expenditures as the number of patients increase
72 as a result of aging of the population. Lifestyle modifications such
73 as fluid restriction and sleep enhancement are expected to be
74 helpful,^{1,2,7} but effectiveness of this strategy has not been
75 established. The aim of this study was to test the efficacy of non-drug
76 lifestyle measures as a first step to treat nocturia. We also sought
77 to find factors predictive of the efficacy of the intervention.

78

79 **Materials and methods**

80

81 Of the patients who visited our outpatient clinic with a chief
82 complaint of nocturia, those with nocturnal frequency of two or more
83 voids were enrolled in this study. Exclusion criteria were post void
84 residual volume of more than 50 ml, untreated urogenital malignancies
85 or renal, cardiac or hepatic failure. The patients who strongly sought
86 medical treatment were also excluded.

87 After completing a 72 h frequency volume chart (FVC), the patients
88 were advised to modify their lifestyle in order to improve nocturia.
89 Lifestyle modifications consisted of four directives - restriction
90 of fluid intake, refraining from excess hours in bed, moderate daily
91 exercise and keeping warm in bed. We paid attention to avoiding
92 imposing too strict measures on the patients, and gave them an
93 explanatory brochure to aid their understanding of the procedure.

94 **In the brochure we said, "Examples of lifestyles that can be associated**
95 **with nocturia are listed below. If you think one or more are applicable**
96 **to you, please follow the appropriate recommendations."** For fluid
97 **restriction, we instructed the patients that daily fluid intake of**
98 **2% of the body weight (i.e., 1000 ml for a person weighing 50 kg)**
99 **is enough. We also told patients to restrict fluid in particular in**
100 **the evening and to avoid excess alcohol or caffeine intake. Secondly,**
101 **we explained that the patients should not stay in bed for a long time**

102 and that excess bedtime hours would make their sleep shallower,
103 leading to worsening of the nocturia. Thirdly, as an example of
104 moderate daily exercise, we told the patients "If you can walk, try
105 to walk 20 minutes a day. Walking in the evening would be more
106 effective." Finally, we suggested taking a hot water bottle to bed
107 as one of the methods to keep warm in bed.

108 The FVC, International Prostate Symptom Score (IPSS)⁸ and Pittsburgh
109 Sleep Quality Index (PSQI)^{9,10} before and 4 weeks after the intervention
110 were used to evaluate the efficacy of the therapy. **The Japanese**
111 **versions of these questionnaires have been validated previously.**^{8,10}
112 **Outcomes were defined as excellent (nocturia decreased by ≥ 2 episodes**
113 **/ night), improved (nocturia decreased by ≥ 1 episode / night), or**
114 **unchanged. We offered further medical therapy to the non-responders.**
115 The PSQI is a self-rated questionnaire for evaluating subjective sleep
116 quality. The questions are combined to obtain a global score ranging
117 from 0-21, with higher scores indicating worse sleep quality. The
118 global score of > 5 is considered to indicate a sleep disorder.⁹

119 Nocturnal urine volume (NUV) was defined as the total volume of
120 urine passed during the night including the first morning void.¹¹
121 Nighttime was defined as the period between going to bed with the
122 intention of sleeping and waking with the intention of rising.¹² From
123 the FVC variables, the following measurements were derived as
124 described elsewhere:¹³ the nocturnal polyuria index (NPi: the ratio

125 of NUV to 24 h urine volume); the nocturia index (Ni: a measure of
126 nocturnal urine overproduction; a higher score indicating a greater
127 nocturnal urine overproduction); the predicted number of nocturnal
128 voids (PNV); and the nocturnal bladder capacity index (NBCi:
129 reflective of nocturnal bladder capacity, a higher score suggesting
130 diminished NBC). The nighttime to daytime diuresis ratio was
131 calculated as $[\text{NUV}(\text{ml}) / \text{nighttime}(\text{h})] / [(24\text{h urine volume} - \text{NUV})$
132 $(\text{ml}) / (24 - \text{nighttime}) (\text{h})]$.

133 For statistical analyses, a Wilcoxon signed rank test was used to
134 compare repeated measurements of variables. Spearman correlation
135 coefficients were used to examine the relationship between baseline
136 parameters and the degree of improvement (change in nighttime
137 frequency). Nominal data were analyzed using the Fisher's exact test.
138 Results were considered significant at $p < 0.05$. Statistical analysis
139 was performed using GraphPad Prism®, version 5.

140

141 **Results**

142

143 Data from 56 patients (47 men and nine women) were evaluated. The
144 mean age was 74.5 ± 5.7 years (range 59-85) **and the mean body mass**
145 **index was 21.8 ± 3.2 (range 15.0 - 30.9).** Underlying medical disorders
146 **included hypertension (13 patients, 23.2 %), diabetes mellitus (12,**
147 **21.4 %), cardiac conditions (10, 17.9 %) and sleep apnea (3, 5.4 %).**

148 Medical prescriptions included alpha-blockers (13, 23.2 %),
149 cholinergics (2, 3.6 %), anti-cholinergics (10, 17.9 %) for lower
150 urinary tract symptoms, and diuretics (5, 8.9 %) for cardiac
151 conditions. We did not change the previously prescribed drugs and
152 just added the lifestyle modifications.

153 Abstracts from the FVC before and after the intervention showed
154 significant objective improvement in the symptoms as shown in Table
155 1. The mean number of nocturnal voids and the NUV decreased from 3.6 ± 1.1 to 2.7 ± 1.2 ml ($p < 0.0001$, Fig. 1) and from 923 ± 332 ml to
156 768 ± 339 ml ($p = 0.0005$), respectively. **The percentage of patients**
157 **with improved and excellent responses was 53.1 % and 24.5 %,**
158 **respectively.** The 24 h frequency of micturition also decreased from
159 11.6 ± 2.6 to 10.7 ± 2.9 times ($p = 0.0065$). Analyses of the FVC-derived
160 variables revealed significant improvement in NP_i, Ni and NBC_i (Table
161 1). The proportion of patients with normal NP_i (less than 33 %¹²)
162 increased from 4% to 20%. The mean nighttime to daytime diuresis ratio
163 decreased from 1.46 ± 0.38 to 1.32 ± 0.43 ($p = 0.0052$).

165 Patient-reported mean number of nocturia episodes (IPSS question
166 7) and IPSS-QOL (quality of life) score significantly decreased after
167 the intervention (Table 2). In 31 out of the 56 patients (54.4%),
168 **the nocturia improved (decreased by ≥ 1 points).** In 28 (50.0%), the
169 IPSS-QOL score improved by 1 or more points. **There were no significant**
170 **changes in the other scores (IPSS 1 through 6) before and after the**

171 **intervention.** Analyses of the PSQI revealed that although the PSQI
172 global score did not show a significant change, the sleep quality
173 score significantly improved after the intervention.

174 **Of the non-responders 52 % (13 / 25) underwent medical therapy,**
175 **which included anti-cholinergics, desmopressin, diuretics, or**
176 **non-steroidal anti-inflammatory drugs. Other non-responders**
177 **continued the lifestyle modifications instead of taking medicine.**

178 Among the baseline parameters tested, 24 h and nocturnal urine
179 volume were significantly associated with the degree of improvement
180 (Fig. 2). In addition, **10 patients (40 %) out of 25 presenting with**
181 **a larger volume of 24 h urine production (greater than the median**
182 **value) achieved an excellent response as compared to only 2 patients**
183 **(8.3 %) out of 24 with less than the median value (Fisher's exact**
184 **test $p = 0.018$). All 12 patients who achieved an excellent response**
185 **were male and none of the female patients showed an excellent response;**
186 **however, it is difficult to draw a definite conclusion about the sex**
187 **difference on the efficacy of the treatment because of the small number**
188 **of female patients.**

189 There was no significant worsening of the health status reported
190 by the patients during this period.

191

192 **Discussion**

193

194 Nocturia is associated with various kinds of medical conditions such
195 as overactive bladder, prostatic disease, diabetes mellitus,
196 cardiovascular disease and sleep disorders.¹ Therapeutic strategies
197 include reducing NUV, increasing nocturnal bladder capacity and
198 treating sleep disorders. Lifestyle modification or behavioral
199 therapy are often mentioned in the literature, mainly in an attempt
200 to reduce nocturnal urine volume; however, their efficacy has not
201 been established and some authors believe that these treatments are
202 of limited efficacy and that pharmacologic therapy is the only option
203 for the majority of patients.⁶ In this study, we attempted to evaluate
204 the efficacy of this strategy by combining four types of lifestyle
205 modifications.

206 The first step in our treatment is fluid restriction. Many people,
207 encouraged by articles in the media, believe that a high water intake
208 will help to prevent ischemic heart disease or cerebrovascular disease
209 and they indeed drink a lot of water; however, there is no definite
210 evidence that stroke or myocardial infarction can be prevented by
211 increasing the water intake in daily life, and that a high intake
212 of water will actually decrease blood viscosity.¹⁴ Reducing fluid
213 intake has already been recommended in patients whose nocturia is
214 secondary to nocturnal polyuria;^{1,15} however, there has been no
215 recommendation stating the actual means of fluid restriction. As total
216 24 h urine volume in healthy individuals was reported to be $23.0 \pm$

217 1.7 ml/kg¹⁶ and this is roughly equivalent to drinking fluid of 2-2.5%
218 of body weight, **we made a recommendation as described in the Methods**
219 **section.**

220 Second, we recommended shortening the time spent in bed to improve
221 sleep quality. We previously reported that patients with nocturia
222 spent a significantly longer time in bed than controls.^{17,18}

223 The third measure was to maintain moderate daily exercise. Asplund
224 and Aberg reported that lack of regular exercise was associated with
225 an increased number of nocturnal micturition episodes,¹⁹ and Sugaya
226 et al. showed the efficacy of walking exercise in the treatment of
227 nocturia.²⁰ By using the protocol of 30 min rapid walking in the evening
228 or night for 8 weeks, they achieved a significant reduction in the
229 number of nocturia episodes from 3.3 to 1.9. It is a very useful
230 behavioral therapy; however, we were afraid that some of the elderly
231 patients would find difficulty in carrying out this practice. In order
232 to make the protocol suitable for as many patients as possible
233 including those with impaired activities of daily living, **we made**
234 **a recommendation of moderate exercise, where possible, as described**
235 **in the Methods section.**

236 Finally, we included a recommendation to keep warm in bed. Cold
237 exposure is known to increase urine output by inducing "cold diuresis"
238 through a combination of increased venous return, activation of atrial
239 natriuretic peptide, decreased levels of antidiuretic hormone and

240 renal antidiuretic hormone receptor, and tubular dysfunction.^{21,22} In
241 our previous study using a self-reported questionnaire on the reasons
242 for change in night time frequency in patients with symptomatic
243 nocturia, feeling cold in bed was the third most prevalent answer
244 next to increased fluid intake and longer duration in bed.¹⁸ We have
245 also shown that urinary symptoms including nocturia worsen in winter
246 in the general population.²³

247 The major limitation of our study is the lack of a control group.
248 Although the gold standard for study design is a randomized controlled
249 trial, it is difficult to set a control group in this kind of study.
250 A possible placebo effect and a patient selection bias should
251 therefore be kept in mind in interpreting the results. Nevertheless,
252 the objective improvements shown in the FVC analyses strongly support
253 the efficacy of the therapy. Another weakness of the study is that
254 **we did not structurally obtain the information about the degree to**
255 **which the patients actually incorporated the behavioral**
256 **recommendations. Although that is an important issue, we did not want**
257 **to frustrate the patients by burdening them with writing down the**
258 **details of their lifestyle in addition to keeping the FVC and answering**
259 **the questionnaires. We decided that the IPSS, PSQI and FVC were the**
260 **minimal requirements to evaluate the efficacy of our therapy. It is**
261 **therefore difficult to assess which component worked best for each**
262 **patient. The most effective and suitable intervention to the given**

263 **baseline conditions should be determined as the next step.** Finally,
264 the long-term effect remains to be confirmed. This point should also
265 be clarified in the future studies.

266 In conclusion, the present study demonstrated that lifestyle
267 measures were effective in improving nocturia, and patients with
268 larger 24 h urine volume showed a better response. Assessment of FVC
269 and FVC-derived variables revealed that the number of nocturnal voids
270 and nocturnal urine volume significantly decreased, and NPi, Ni and
271 NBCi significantly improved after the intervention; however, bladder
272 capacity did not show any significant change. This implies that the
273 efficacy of this therapy is primarily attributable to the reduction
274 of nocturnal urine volume.

275

276 **Conclusions**

277

278 Non-drug lifestyle measures were effective in reducing the number
279 of nocturia episodes and improving patients' QoL. The effect of this
280 therapy was shown to result from a reduction in NUV. Patients with
281 polyuria showed a better response to the treatment.

282

283

284 **Abbreviations**

285 FVC: frequency volume chart

286 IPSS: International Prostate Symptom Score
287 NBCi: nocturnal bladder capacity index
288 Ni: nocturia index
289 NPi: nocturnal polyuria index
290 NUV: nocturnal urine volume
291 PNV: predicted number of nocturnal voids
292 PSQI: Pittsburgh Sleep Quality Index
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356

357 **Figure Legends**

358 **Fig. 1 – Box plots showing nocturnal frequency before and after the**

359 **intervention.** Whiskers: 10-90 percentiles; $p < 0.001$.

360 **Fig. 2 – The relationship between pre-treatment 24 h urine volume**

361 **(A) and nocturnal urine volume (B) and decreased number of nocturia**

362 **episodes.** A: $r = 0.3923$; $p = 0.0102$; B: $r = 0.3088$; $p = 0.0466$.

363

TABLES

Table 1 – Results of frequency volume chart before and after the intervention

Variables	Before	After	<i>p</i>
NUV, ml			
Mean (SD)	923 (332)	768 (339)	
Median (range)	917 (235-1650)	707 (175-1513)	< 0.001
24 h UV, ml			
Mean (SD)	1850 (581)	1716 (607)	
Median (range)	1835 (665-3537)	1705 (675-3084)	0.024
Nocturnal frequency			
Mean (SD)	3.6 (1.1)	2.7 (1.2)	
Median (range)	3.6 (2.0-6.5)	2.8 (0.3-5.0)	< 0.001
24h frequency			
Mean (SD)	11.6 (2.6)	10.7 (2.9)	
Median (range)	11.3 (6.3-19.5)	10.0 (5.3-18.5)	0.007
MVV, ml			
Mean (SD)	309 (99)	313 (103)	
Median (range)	300 (50-530)	300 (50-600)	0.65
NPi			
Mean (SD)	50.5 (12.2)	45.9 (14.7)	
Median (range)	48.3 (25.2-75.4)	45.0 (14.6-72.6)	0.004
Ni			
Mean (SD)	3.1 (0.9)	2.6 (0.9)	
Median (range)	2.9 (1.4-5.4)	2.6 (1.2-4.3)	< 0.001
NBCi			
Mean (SD)	1.5 (0.7)	1.3 (0.6)	
Median (range)	1.6 (0.2-3.7)	1.2 (0.1-2.8)	0.002

N/D diuresis ratio

Mean (SD)	1.46 (0.38)	1.32 (0.43)
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Median (range)	1.44 (0.64-2.52)	1.31 (0.58-2.19)	0.005
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NUV = nocturnal urine volume; MVV = maximum voided volume; NPi

= nocturnal polyuria index; Ni = nocturia index; NBCi= nocturnal

bladder capacity index

TABLES

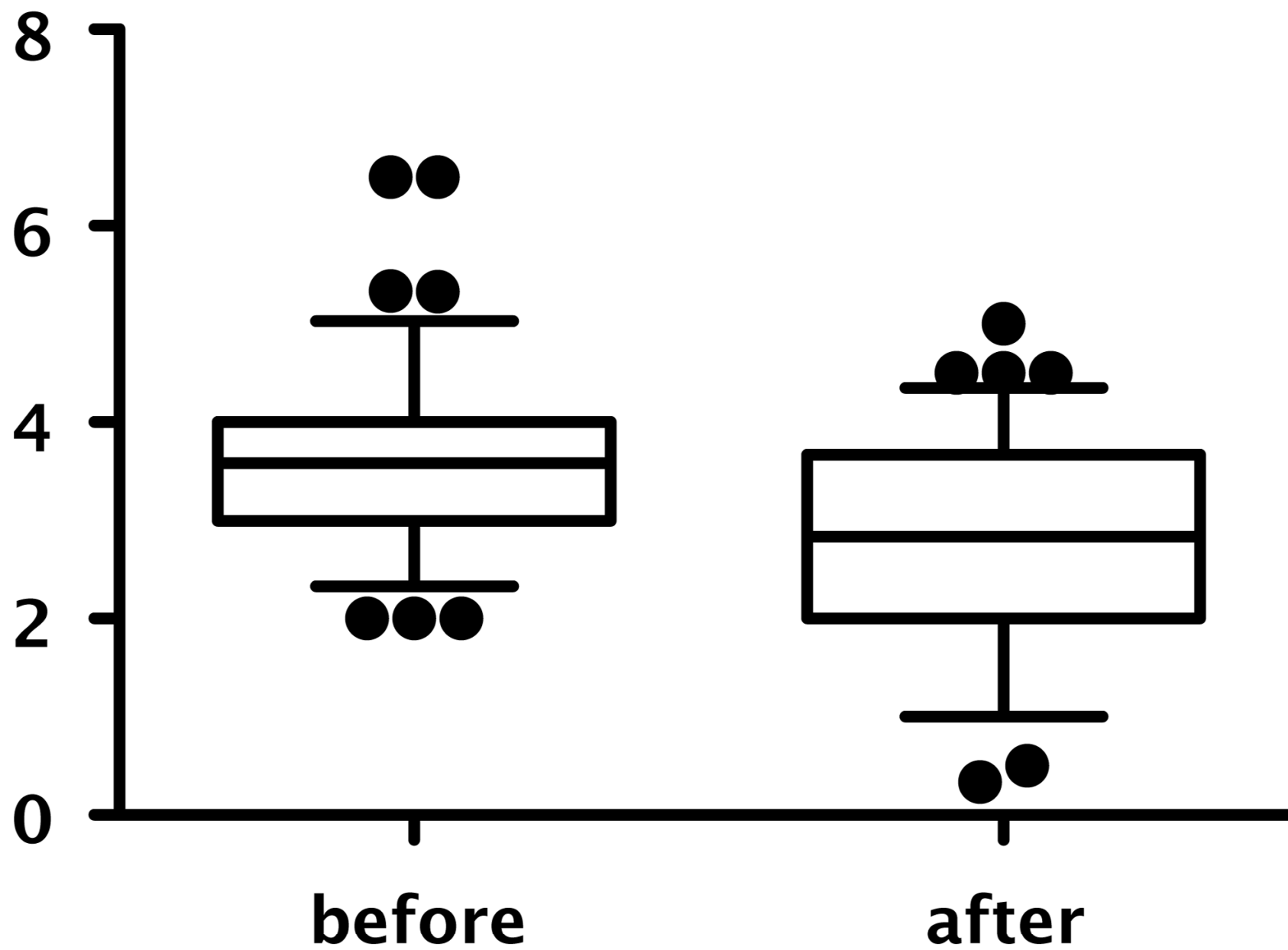
Table 2 – Results of IPSS and PSQI before and after the intervention

Variables	Before	After	p
IPSS - 7			
Mean (SD)	3.8 (0.8)	3.1 (1.2)	
Median (range)	4.0 (2.0-5.0)	3.0 (1.0-5.0)	<0.001
IPSS - QOL			
Mean (SD)	4.6 (1.0)	3.8 (1.4)	
Median (range)	5.0 (2.0-6.0)	4.0 (0.0-6.0)	<0.001
PSQIG			
Mean (SD)	6.56	5.95	
Median (range)	6.0 (0.0-14.0)	5.0 (0.0-14.0)	0.25
Sleep quality			
Mean (SD)	2.43 (0.80)	2.10 (0.72)	
Median (range)	2.0 (1.0-4.0)	2.0 (1.0-4.0)	0.007
Time in bed, hours			
Mean (SD)	8.44 (1.1)	8.38 (1.2)	
Median (range)	8.5 (6.0-10.5)	8.5 (6.2-11.3)	0.99

IPSS = International Prostate Symptom Score; PSQIG = Pittsburgh

Sleep Quality Index global score

number of nocturia episodes



Decreased number of
nocturia episodes

