

A COMBINATION THERAPY WITH LOW DOSE DESMOPRESSIN AND TOLTERODINE IMPROVES HEALTH-RELATED QUALITY OF LIFE IN FEMALE PATIENTS WITH OVERACTIVE BLADDER AND NOCTURNAL POLYURIA

Hypothesis / aims of study

Studies have shown that patients with overactive bladder (OAB) and nocturia, particularly nocturnal polyuria (NP), have a compromised health-related quality of life (HRQoL). Furthermore, NP is also associated with a poor quality and quantity of sleep, thereby significantly impacting day-time activity, performance, and mood. An association between the number of nocturnal voids and quality of sleep was also reported (1). Therefore, a treatment that addresses NP in these patients is warranted. The current posthoc analysis on patients participating in a large randomised, double-blinded trial was undertaken to determine whether combining tolterodine with low dose desmopressin, an antidiuretic, reduces the nocturnal volume and thereby frequency and urgency of nocturnal voids resulting in an improved HRQoL in these patients. For this, patients were categorised into NP (nocturnal volume $\geq 33\%$ of total daily urine volume at Baseline) and non-NP subgroups (nocturnal volume $< 33\%$ of total daily urine volume at Baseline). The effect of combination therapy on HRQoL was assessed by evaluating the change in scores of Nocturia Impact (NI) Diary[®] (2) and three Sleep Quality Rating scales.

Study design, materials and methods

The present posthoc analysis included 94 adult female patients with OAB and nocturia, where patients received a low dose desmopressin 25 μ g and tolterodine 4 mg (combination therapy) or tolterodine 4 mg alone (monotherapy), once daily at bedtime, for 3 months. Patients had to have ≥ 2 but < 10 nocturnal voids per day. In the NP subgroup, there were 47 patients in the FAS (25 in combination therapy and 22 in monotherapy group) and 41 patients in the PP analysis set (21 in combination therapy and 20 in monotherapy group). In the non NP subgroup, there were 47 patients in the FAS (20 in combination therapy and 27 in the monotherapy group) and 45 patients in the PP analysis set (20 in combination therapy and 25 in monotherapy group).

The daily impact of nocturia was evaluated by the NI Diary[®], which is a 12-item instrument consisting of 11 core items (Q1-Q11) and an overall quality of life (QoL) impact question (Q12; Does nocturia impact your life?). Q1 to Q11 include effect of nocturia on day-time concentration, energy, productivity, activities, mood, fluid restriction, difficulty in sleeping after nocturnal void, feeling of having little sleep, fear of falling, fear of worsening nocturia, and fear of not finding the bathroom when away from home overnight. Responses were scored from 0 (lowest impact) to 4 (highest impact). The NI total score was calculated by summing the 11 core items. The NI total score and the overall impact question were standardized from 0 (lowest impact) to 100 (highest impact). Also evaluated was the impact on sleep using three Sleep Quality Rating scale questions in the 3 day void/sleep diary: 1. On a scale from very tired to wide-awake, how do you feel right now? 2. Rate how refreshed you feel? 3. Rate the quality of your sleep last night. The responses were rated on a scale of 1 (poor) to 10 (good) between the two treatment groups. An electronic diary (eDiary) was used to document these parameters. The change from Baseline for NI Diary[®] scores, and impact on sleep quality were analyzed using analysis of covariance with a longitudinal analysis of the three months of treatment. The minimally important difference for NI Diary[®] total scores (unidimensional) was set at a change of half a standard deviation (SD) as recommended previously (3).

Results

The results in the NP subgroup showed that there was a greater improvement from Baseline in the NI Diary[®] total scores (Q1 to Q11) in the combination therapy versus tolterodine monotherapy, reaching statistical significance in the PP analysis set. Similarly, the NI Diary[®] score for overall QoL impact question (Q12) showed that there was a greater improvement with combination therapy versus tolterodine monotherapy, though this did not reach statistical significance. In the non NP subgroup, the change in NI Diary[®] total and impact scores, and QoL question scores were comparable between the two treatment groups (FAS and PP analysis set). The results are presented in Figure 1.

The numerical improvement in mean quality of Sleep Rating scales were also generally more in favour of the NP population treated with the combination therapy ([FAS: range 0.48-0.62 for NP and range -0.08 to 0.27 for non-NP subgroups] and [PP analysis set: range 0.64-0.84 for NP and range -0.05 to 0.39 for non-NP subgroups], $p > 0.05$ for both the analyses sets).

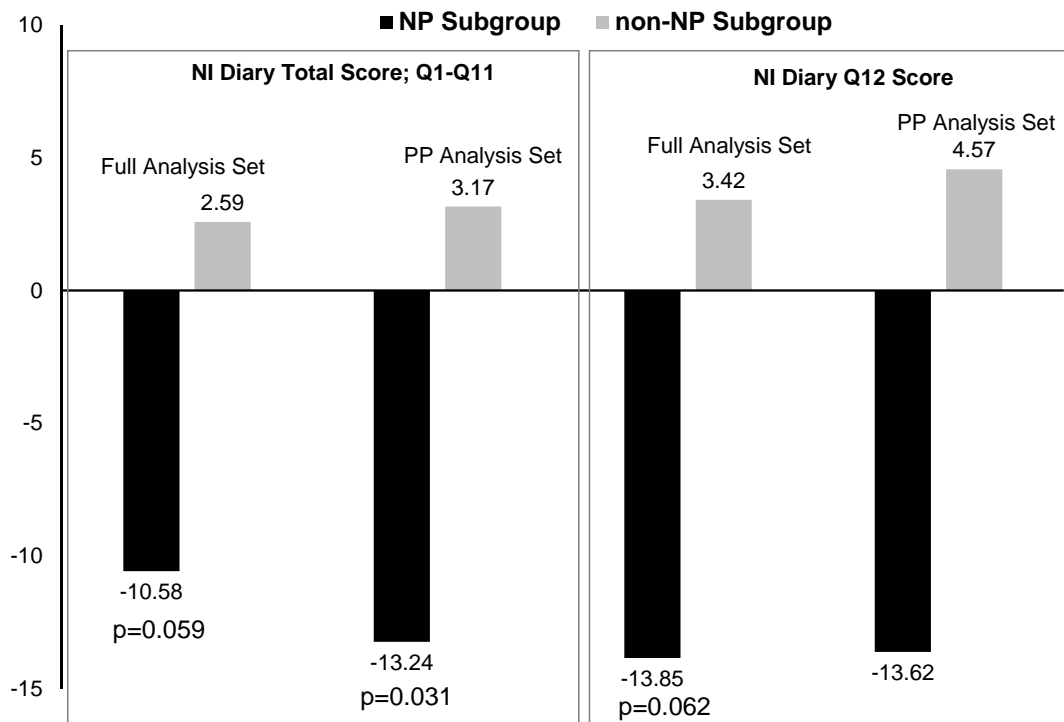
Interpretation of results

The combination therapy demonstrated improved HRQoL that exceeded that of antimuscarinic monotherapy in NP subgroup. However, there was apparently no additional benefit with combination therapy in the non-NP subgroup. Also, there was a trend towards improvement in the sleep quality with combination therapy versus tolterodine monotherapy in the NP subgroup. This indicates a subset selectivity where patients with NP significantly benefitted from combination therapy, which is in-line with the antidiuretic mechanism of action of desmopressin, which reduces the nocturnal volume hence reducing the need to void. The results also support the use of the NI Diary[®] in assessing the daily impact of nocturia in patients with OAB and nocturia. The improvement in NI Diary[®] scores is above the clinically important threshold which has been estimated to be around 10 points by the developers (1), and also using the recommended statistical approach of $\frac{1}{2}$ SD (3).

Concluding message

This analysis indicates that desmopressin combined with tolterodine improves HRQoL in patients with OAB and nocturia, and that an additional clinical benefit can be expected for patients with NP. However, this needs to be further explored in prospective studies powered adequately to detect such a difference.

Figure 1. Treatment Contrasts for NI Diary® Scores between the Combination and Monotherapy



References

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3. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Med Care.* 2003;41(5):582-92.

Disclosures

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 2. Medical University of South Carolina, Institutional Review Board for Human Research, Charleston, South Carolina
 3. NorthShore University HealthSystem, Institutional Review Board, Evanston, IL
 4. Quorum Institutional Review Board, Lower Gwynedd, PA **Helsinki:** Yes **Informed Consent:** Yes