



Use of Structural Equation Modeling to Demonstrate the Differential Impact of Storage and Voiding Lower Urinary Tract Symptoms on Symptom Bother and Quality of Life during Treatment for Lower Urinary Tract Symptoms Associated with Benign Prostatic Hyperplasia

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Abbreviations and Acronyms

BPH = benign prostatic hyperplasia
CFI = comparative fit index
GFI = goodness of fit index
LUTS = lower urinary tract symptoms
PTCF = probability for test of close fit
 Q_{max} = maximum urinary flow rate
QoL = quality of life
RCT = randomized, controlled trial

Purpose: Lower urinary tract symptoms associated with benign prostatic hyperplasia typically respond well to medical therapy. While changes in total I-PSS (International Prostate Symptom Score) are generally accepted as measurement for treatment response, I-PSS storage and voiding subscores may not accurately reflect the influence of symptom improvement on patient bother and quality of life.

Materials and Methods: Structural equation modeling was done to evaluate physiological interrelationships measured by I-PSS storage vs voiding subscore questions and measure the magnitude of effects on bother using BII (Benign Prostatic Hyperplasia Impact Index) and quality of life on I-PSS quality of life questions. Pooled data from 4 randomized, controlled trials of tadalafil and placebo in 1,462 men with lower urinary tract symptoms/benign prostatic hyperplasia were used to investigate the relationship of storage vs voiding lower urinary tract symptoms on BII and quality of life.

Results: The final structural equation model demonstrated a sufficient fit to model interdependence of storage, voiding, bother and quality of life (probability for test of close fit <0.0001). Storage aspects had a twofold greater effect on voiding vs voiding aspects on storage (0.61 vs 0.28, each $p <0.0001$). The direct effect of storage on bother was twofold greater than voiding on bother (0.64 vs 0.29, each $p <0.0001$). Bother directly impacted quality of life by the largest magnitude of (-0.83), largely driven by storage lower urinary tract symptoms ($p <0.0001$).

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Conclusions: Total I-PSS is a reliable instrument to assess the therapeutic response in lower urinary tract symptoms/benign prostatic hyperplasia cases. However, an improvement in storage lower urinary tract symptoms is mainly responsible for improved bother and quality of life during treatment. Care should be taken when evaluating the accuracy of I-PSS subscores as indicators of the response to medical therapy.

Key Words: prostate, prostatic hyperplasia, lower urinary tract symptoms, quality of life, patient-specific modeling

LOWER urinary tract symptoms associated with BPH are bothersome and prevalent in older men.^{1,2} The advent of medical therapy for LUTS/BPH in the 1990s changed the treatment paradigm, enabling men who had a significant symptom burden but were reluctant to undergo prostate surgery to benefit from therapy. These pharmacological options were accompanied by publication of the first validated symptom questionnaire, I-PSS,³ which is the standard patient reported outcome instrument for regulatory approval and evidence supporting specialty society LUTS/BPH therapeutic guidelines.^{4–6}

Since the introduction of medical therapy for LUTS/BPH, bladder storage LUTS (eg urgency, daytime frequency and nocturia) have been recognized to cause a greater reduction in QoL than voiding LUTS (eg hesitancy, poor urinary stream and intermittence).^{7–9} Storage LUTS appear to be most bothersome.¹⁰ They also contribute to a greater disease specific QoL decrease in men with LUTS/BPH¹¹ and more tightly correlate with QoL across all treatment modalities.¹²

Despite the demonstrated value of total I-PSS reduction as evidence of clinical benefit during therapy attempts to document the differential impact of a storage vs a voiding LUTS reduction on patient improvement have failed. While total I-PSS questionnaire validation is documented and well accepted, storage subscores (the sum of I-PSS questions 2, 4 and 7) and voiding subscores (the sum of I-PSS questions 1, 3, 5 and 6)¹³ remain unvalidated and it remains to be determined whether a relationship exists between these subscores.¹⁴ Using a pooled 4-study, placebo controlled database Chapple et al assessed relationships of total I-PSS to storage and voiding subscores in men with LUTS/BPH and evaluated whether storage and voiding correlated independently with improvements in storage and voiding I-PSS ratios.¹⁴ Their analyses did not document such a relationship, a limitation attributable to the lack of validation of storage and voiding subscores.

We believe that total I-PSS accurately measures the therapeutic response in patients treated for LUTS/BPH. However, I-PSS was not designed to separately measure the differential impact of

storage vs voiding LUTS on bother, QoL and treatment satisfaction.

Structural equation modeling is a well accepted but largely unknown statistical method in urology. It assesses how latent (unobserved) variables that are difficult to measure relate to each other and to observed measures that are the result of latent variables.¹⁵ Structural equation modeling incorporates multi-equation models, multiple measures of latent variables in the model and measurement error. Importantly, unlike multiple regression and ANCOVA, the structural component in structural equation modeling assigns causal assumptions to the model.

In this analysis using a clinical RCT database we performed structural equation modeling to investigate the amount to which storage LUTS captured by I-PSS changes differentially drive overall LUTS improvement, symptom bother and QoL in men with LUTS/BPH.

PATIENTS AND METHODS

Study Design, Data Set and Analysis

We performed a priori, specified, structural equation modeling analysis to assess relationships between observed variables (age, tadalafil or placebo treatment, 7 single I-PSS items, the I-PSS-QoL question and 4 single BPH BII items) and latent variables (storage and voiding anatomic/physiological parameters, I-PSS subscores and total BII). We defined a structural equation modeling model using our clinical understanding of the relationship of storage/voiding symptoms and factors associated with LUTS. Using structural equation modeling allowed for the determination of direct and indirect effects between observed and latent variables. The effects of variables were estimated using a pooled database (tadalafil and placebo) from 4 RCTs in men with LUTS/BPH.^{16–19}

The 4 RCTs shared largely similar designs, durations, study populations and inclusion/exclusion criteria.^{16–19} A 4-week single-blind placebo lead-in period was followed by a 12-week double-blind treatment phase. This data set included only patients who received once daily tadalafil 5 mg or placebo. The primary outcome was the improvement in total I-PSS from baseline to end point (week 12). Study inclusion/exclusion criteria have been previously described.^{16–19} Subjects were 45 years old or older with a greater than 6-month history of LUTS/BPH, I-PSS 13 or greater and Q_{max} 4 to 15 ml per second.

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