Chapter 4: Research and Future Directions

Introduction

Many of the future research needs listed in the 1994 Agency for Health Care Policy and Research (AHCPR) clinical practice guideline *Benign Prostatic Hyperplasia Diagnosis and Treatment*[1] have been addressed in the past 9 years. Knowledge of the natural history and epidemiology of lower urinary tract symptoms (LUTS) and benign prostatic hyperplasia (BPH) has increased substantially, and understanding of the efficacy and safety of medical interventions is significantly greater thanks to a multitude of well-planned and well-executed clinical trials, mostly randomized and placebo-controlled in design. However, despite these advances, some of the issues raised then still remain controversial now while other concerns and knowledge gaps have arisen.

What seemed to be simple in 1994 has now become a major controversy, that is, the naming of the condition that is studied, diagnosed and treated. As discussed in Chapter 1, the term "benign prostatic hyperplasia" has been criticized as being too specific. The term that is now widely accepted is "lower urinary tract symptoms," which correctly focuses attention on the irritative and obstructive symptoms that are at the center of the diagnostic and therapeutic efforts[120, 121]. In most cases, histological evidence for hyperplasia is lacking. Therefore, the term BPH might either be restricted to those with histological verification or be amended as "clinical BPH," indicating that the diagnosis is based on the most likely clinical scenario[122].

Recent research endeavors have led to new insights as well as to new questions. For example, the development of new, so-called uroselective, alpha-receptor blockers has led to the realization that symptomatic relief is not exclusively induced by blockade of the $alpha_{1a}$ receptors in the

bladder neck and prostate areas. Rather, central-acting effects are suspected to be involved in the efficacy of such drugs[123]. New indications have emerged for the 5 alpha-reductase inhibitor agents based on their ability to interfere with angiogenesis and vascularity in the prostate[124, 125], raising questions regarding their mechanisms of action. Results of research concerning the use of phytotherapeutic agents for the treatment of BPH are being reported regularly[126-129]. The proposed mechanisms of action are numerous and appear to vary from agent to agent and over time, with basic high-quality research data lacking. The palette of minimally invasive surgical treatments for BPH is constantly evolving as the treatments increase in popularity, but a fundamental understanding of the heat-based mechanisms of action is still lacking.

Etiology and pathophysiology

The two widely accepted etiological factors contributing to the development of BPH, aging and functional testes, clearly represent an inadequate and incomplete theoretical construct. In order to develop new and more effective agents for treatment, research is needed to understand and define the roles of the following:

- *intrinsic* factors, such as stromal-epithelial interaction and the extracellular component of the prostate;
- various growth factors implicated in the etiology and pathogenesis of BPH;
- *extrinsic* factors, such as sex hormones (androgens and estrogens), and other somatic and environmental factors;
- genetic factors;
- various factors that contribute to the irritative and obstructive aspects of LUTS, including the prostate and bladder as well as central mechanisms; and
- the aging bladder/detrusor muscle in the pathogenesis of LUTS.

Natural history and epidemiology

The "Olmsted County Study of Urinary Symptoms in Men" has contributed immensely to our understanding of the natural history and epidemiology of BPH [32, 110, 107, 130-134]. In addition, natural history studies conducted in various countries and in different ethnic groups have enhanced our knowledge, although the majority of such studies were cross-sectional rather than longitudinal in design. Longitudinal data from large placebo control groups followed for up to 4 years also have proven to be valuable sources of information[112, 20, 109, 34]. The following are areas that warrant future research efforts:

- establishing a working epidemiological definition of BPH that is accepted worldwide to replace descriptions of distributions of individual signs and symptoms in the population;
- studying the rates of outcomes, such as acute urinary retention, infection, bladder deterioration and upper tract deterioration, in age-stratified men, in different ethnic populations and in different environments using established criteria;
- identifying baseline parameters that can be used to predict the incidence of such outcomes over time;
- studying community-based occurrences of concomitant urological conditions, such as LUTS, erectile dysfunction and incontinence, as well as other conditions, such as hypertension and vascular diseases;
- detailing studies of familial and genetic aspects of BPH; and
- focusing on prevention of outcomes, progression and/or development of BPH in high-risk patients and/or the population at large.

Diagnosis and initial management

The 1994 AHCPR guideline made several recommendations regarding the appropriateness of diagnostic testing, which led to a change in the practice pattern of most urologists. However, while some issues are still unresolved, the value of certain tests should be reevaluated in light of new clinical insights. In particular, the following need to be determined:

- whether or not the widely accepted American Urological Association Symptom Index/International Prostate Symptom Score (Appendix 1-A) needs to be changed or enhanced through additional questions (e.g., regarding incontinence) or whether it is being used in general practice and improves patient care;
- whether or not instruments measuring bother, interferences and quality of life are more valuable than those that measure symptom frequency and severity alone; and
- the predictive value of symptom, bother, quality-of-life assessments, serum prostate-specific antigen, prostate volume, flow-rate recording, residual urine, imaging studies, cystoscopy, pressure-flow urodynamic studies and other tests in terms of
    - natural history,
    - progression of disease, and
    - response to various interventions.

Therapeutic interventions

The therapeutic armamentarium has changed considerably since 1994. Balloon dilation is no longer practiced but other minimally invasive surgical treatment alternatives are available, and new alpha-adrenergic blockers, a new 5 alpha-reductase inhibitor, as well as phytotherapeutic agents are enjoying widespread use. However, several research needs are pressing:

- continuing to study untreated or placebo-treated patients over prolonged periods to enhance understanding of symptom changes, as well as to establish the incidence of complications and of adverse outcomes;
- determining the exact mechanism(s) of action of therapeutic interventions such as those mentioned earlier;
- developing accepted and standard worldwide definitions of "treatment failure" and "retreatment rates" to allow such rates to be compared across therapies;
- developing protocols and conducting direct comparator trials, including control arms (placebo or known active), to better understand the presence and/or magnitude of differences between similar interventions; and
- establishing a centralized, international data repository to store clinical trial data for future comparison and analyses.

Economics

With regard to economic issues, the following remain as research needs:

- determine the cost-effectiveness of diagnostic tests, such as laboratory and imaging studies, cystoscopy and urodynamic testing;
- collect cost data as part of clinical trials in the same manner as clinical data are collected, including direct and indirect cost, loss of productivity, time spent by patients, and so on;
- incorporate cost comparisons in randomized, clinical trials that compare competing therapeutic interventions; and
- quantify and compare the “values” associated with numerical improvements in symptoms, bother, quality of life, flow rate, urodynamic parameters, prevention of complications and other outcomes.

Reporting and publication issues

Despite the increasing number of properly planned and executed randomized, clinical trials in the literature, extraction of data for comparison and meta-analysis remains a challenge due to a lack of reporting and publication standards. In many cases, key statistical data are missing, preventing proper data extraction and analyses.

Reporting and publication standards are needed for the following reasons:

- to ensure that researchers present baseline and endpoint data and provide measures of central tendency (mean or median) and variance (standard error, standard deviation [SD] with indication as to whether the SD is from the sample that is preferred or is an estimate of the population SD, or 95% confidence intervals);
- to ensure that researchers capture and report both absolute and percentage changes for all pertinent numerical outcome data (including measures of central tendency and variance for each) because of uncertainty about which type of data are more relevant;
- to establish common time points to measure outcomes, common classes of adverse events and common subranges for scaled outcomes (e.g., low, medium and high symptom scores, ranges for peak flow, and so on);
- to ensure that a full description is provided of any adjustment of raw data in the statistical analysis and possibly request that unadjusted figures also be provided; currently, it is not uncommon for authors to present only "adjusted" results and not describe what adjustment was done;
- to make certain that researchers report precise p values (not $p <$ or n.s. [not significant]) and variance data (whether $x \pm y$ means standard error of the mean, population standard

deviation [divided by n-1] or sample standard deviation [divided by n] and whether variance estimates reflect population or sample data);

- to establish a uniform method for reporting complications, that is, total number of occurrences versus number of patients who have at least one occurrence;
- to encourage the reporting of backup data tables in survival analyses rather than relying solely on the presentation of Kaplan-Meier curves; and
- to achieve consensus among the editorial boards of all major urological journals regarding reporting and publication standards.

A blueprint for reporting results of a randomized, clinical trial is provided in Appendix 4-A[135].

Appendix 4: A Blueprint for Reporting Results of a Randomized Clinical Trial

Title

"Six-month results of a randomized, sham-controlled, multicenter trial of transurethral microwave thermotherapy (TUMT®) in patients with lower urinary tract symptoms and enlarged prostate glands"

Authors

Names
Affiliations
Address for correspondence
Statement of conflict/Financial interest (for each author)

Abstract

Background and objectives
Materials and methods
Results
Conclusions
Key words
Word count for abstract and manuscript

Introduction

Background of disease or condition studied
Intervention tested
Brief review of available data on intervention or similar treatments
Objective of the current study

Materials and methods

Device/Intervention/Drug/Protocol
Description of the therapeutic intervention

Patient population

Describe population as accurately as possible/needed. Example:

> "This study enrolled patients over the age of 50 years with moderate to severe (more than 12 points on the International Prostate Symptom Score [IPSS]) lower urinary tract symptoms (LUTS), enlarged prostate gland (EPG) by digital rectal examination and suspected bladder outlet obstruction (BOO) based on a peak urinary flow rate of less than 12 mL/sec at a voided volume of > 125 mL. Serum prostate-specific antigen (PSA) had to be under 10 ng/mL, and prostate cancer had to be excluded to the satisfaction of the investigator. Prostate volume was assessed by transrectal ultrasound (TRUS) and had to be between 25 and 100 mL. Patients were randomized at a ratio of 2:1 to active TUMT versus sham treatment. At baseline the populations were well matched (Table 1)."

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Method of blinding

Describe the method of blinding, ways in which success of blinding was assessed and numerical success of blinding.

Outcome parameters and endpoints

List primary, secondary and, if indicated, tertiary endpoints
List other assessments that were made and are relevant to intervention
Describe method in which adverse events/complications were assessed

Follow-up and disposition

Describe the study plan, time points of follow-up, tests and interventions performed at each visit and present data regarding patients' disposition in written form and/or in a flow diagram (Figure 1)

Statistical methods

Sample size and power calculation
Alpha error and level of significance
Tests used to compare within and between group differences:
- parametric versus non-parametric tests,
- special tests applied (multivariate analysis, regression analysis, etc.), and
- software programs used for statistical analysis and/or graphics

Results

Base endpoints on changes to a scaled or continuous measure. For primary, secondary and perhaps additional endpoints present data in tabular or figure format (Tables 1 through 4 and Figures 2 through 4):

- At Baseline:
  - Measure of central tendency:
    - mean or median
  - Measure of variance:
    - standard error or deviation,
    - confidence interval (95% CI), and
    - minimum and maximum (range)
  - Number of patients available

- At time point(s) of follow-up:
  - Measure of central tendency:
    - mean or median
  - Measure of variance:
    - standard error or deviation,
    - confidence interval (95% CI), and
    - minimum and maximum (range)
  - Number of patients available

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Changes from baseline (should be presented as absolute and percentage change):
- Measure of central tendency:
  - mean or median
- Measure of variance:
  - standard error or deviation,
  - confidence interval (95% CI), and
  - minimum and maximum (range)

Statistical tests:
- Appropriate test to determine whether change from baseline is significant *within* each treatment group
- Appropriate test to determine whether the baseline data and data at follow-up *between* groups are significantly different

Report adverse events/complications:
- Present in tabular form, list number of adverse events and/or number of patients with adverse events (see sample Table 5)
- Report adverse events in blocks of time and total to allow assessment of time course
- Report occurrences of adverse events in relation to exposure time (patient-months of exposure); the number at risk at each time point should be stated

Comments/conclusions

Comment on all results reported in the "Results" section in the same sequence as presented in the "Methods" section, for example, report results pertaining to IPSS, peak flow rate, other endpoints, adverse events and so on, then comment on these data in the same sequence in the "Comments/Conclusions" section. For example**:**

In **results:** "On average, peak flow rate improved from 7.6 to 10.7 mL/sec by an average (± sample SD) margin of 2.9 ± 3.3 mL/sec following TUMT treatment, which was significantly better than the average margin of improvement in the sham treatment group of 1.45 ± 3.1 mL/sec."

In **comments:** "Although the margin of improvement in peak flow rate was numerically twice as high in the TUMT versus the sham group, it was not substantially greater than reported for other minimally invasive interventions or even alpha-blocking agents."

Put data and findings in context with other studies using the same intervention, similar intervention, and other interventions. If appropriate, attempt an assessment of cost versus benefits.

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Examples of tables

Table 1: IPSS: Mean ± SD (sample standard deviation) and range for active TUMT and sham treatment groups at baseline and at six-month follow-up, absolute and percent changes from baseline. Shown also are the numbers of patients available for follow-up and the *P*-values for within groups (t test for comparison from baseline) and between groups (t test for comparison between groups).

	TUMT		Sham		Comparison Between Groups
Baseline	n = 147	23.6 ± 5.6 12 – 35	n = 73	23.8 ± 5.6 13 – 35	n.s.
6 Months	n = 143	12.9 ± 7.2 2 – 30	n = 70	17.7 ± 7.6 1 – 35	*P*<0.05
Change		-10.8 ± 7.6 - 29 – 13		-6.0 ± 6.8 -30 – 4	*P*<0.05
% Change		-44 ± 0.3 -93 – 76		-25 – 2.6 -97 – 16	*P*<0.05
% Change from Baseline Within Group		*P*<0.05		*P*<0.05	

Table 2: Peak flow rate: Mean ± SD (sample standard deviation) and range for active TUMT and sham treatment groups at baseline, six month follow-up, absolute and percent changes from baseline. Shown also are the numbers of patients available for follow-up and the *P*-values for within groups (t test for comparison from baseline) and between groups (t test for comparison between groups).

	TUMT		Sham		Comparison Between Groups
Baseline	n = 147	7.6 ± 1.9 3.5 – 11.5	n = 73	8.2 ± 2.1 4.0 – 11.9	n.s.
6 Months	n = 143	10.7 ± 3.8 3.6 – 23	n = 69	9.7 ± 3.4 4.3 – 21.5	*P*<0.05
Change		2.9 ± 3.3 -3.3 – 14.4		1.45 ± 3.1 -4 – 11.5	*P*<0.05
% Change		41.1 ± 0.5 -40 – 210		20.9 ± 0.4 -38 – 155	*P*<0.05
% Change from Baseline Within Group		*P*<0.05		n.s.	

If appropriate categories exist, consider presenting a shift table to indicate the absolute and/or percentage of patients in each category/status at baseline and at endpoint.

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Table 3: TUMT versus Sham: TUMT-treated patients: Number (top) and percent (bottom) of patients at baseline by flow rate status and at six month follow-up. The rows represent patients who "shifted" from the baseline status to another status or who remained in the same status (number and percent). The last row and first column represent total patients stratified by status in number and percent.

Status at Baseline	n	Status at 6-Month Follow-up			
		≤10 mL/sec	10-15 mL/sec	≥15 mL/sec	Lost
≤10 mL/sec	129	71	40	15	3
10-15 mL/sec	18	2	11	4	1
≥15 mL/sec	0	0	0	0	0
Totals	147	73	51	19	4

Status at Baseline	% of Total	Status at 6-Month Follow-up (percent)			
		≤10 mL/sec	10-15 mL/sec	≥ 15 mL/sec	Lost
≤10 mL/sec	87.8	55.0	31.0	11.6	2.3
10-15 mL/sec	12.2	11.1	61.1	22.2	5.6
≥15 mL/sec	0	0.0	0.0	0.0	0.0
Totals	147	49.7	34.7	12.9	2.7

Table 4: TUMT versus Sham: Sham-treated patients: Number (top) and percent (bottom) of patients at baseline by symptom status and at six months follow-up. The rows represent patients who "shifted" from the baseline status to another status or who remained in the same status (number and percent). The last row and first column represent total patients stratified by status in number and percent. For example, at baseline there were 12 (16.4%) moderate and 61 (83.6%) severe patients while at follow-up there were 6 (8.2%) mild, 34 (46.6%) moderate and 30 (41.1%) severe patients.

Status at Baseline	n	Status at 6-Month Follow-up			
		Mild	Moderate	Severe	Lost
Mild (0-7)	0	0	0	0	0
Moderate (8-18)	12	3	8	1	0
Severe (19-35)	61	3	26	29	3
Totals	73	6	34	30	3

Status at Baseline	% of Total	Status at 6-Month Follow-up (percent)			
		Mild	Moderate	Severe	Lost
Mild (0-7)	0	0	0	0	0
Moderate (8-18)	16.4	25.0	66.7	8.3	0.0
Severe (19-35)	83.6	4.9	42.6	47.5	4.9
Totals	73	8.2	46.6	41.1	4.1

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Table 5: Adverse events (A to D) in a double-blind, sham-controlled, six-month TUMT trial for LUTS/EPG/ BOO/BPH. Listed are the number of patients available for follow-up, the episodes of occurrence for the four adverse events within each time period of follow-up and the total number of occurrences during the treatment related to the total number of patient-months (= sum of the number of months that each patient received treatment) expressed as percentages.

	1-month visit		3-month visit		6-month visit		Occurrences per patient-months	
	TUMT n =147	Sham n = 73	TUMT n = 144	Sham n = 71	TUMT n = 143	Sham n = 69	TUMT PM = 862	Sham PM = 422
A	12	6	9	4	8	3	29 / 3.3%	13 / 3.1
B	8	2	7	1	6	1	21 / 2.4	4 / 1.0
C	2	0	5	1	10	1	17 / 1.9	2 / 0.5
D	1	1	1	0	0	1	2 / 0.2	2 / 0.5

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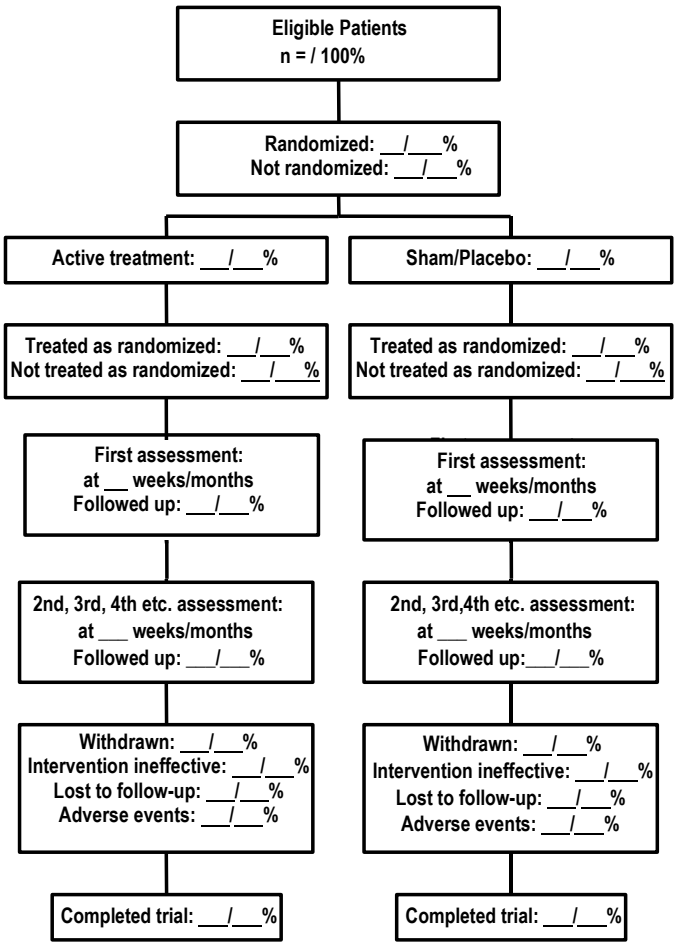
Examples of figures

Figure 1: Flow Diagram of Patient Disposition



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Consider graphical presentation of data:

Grouped bar graphs for numerical outcomes
Cumulative frequency distribution for numerical primary/secondary outcomes

Figure 2: TUMT versus Sham: Changes in American Urological Association Symptom Index (AUA SI) Score Over Time (BL-Baseline)

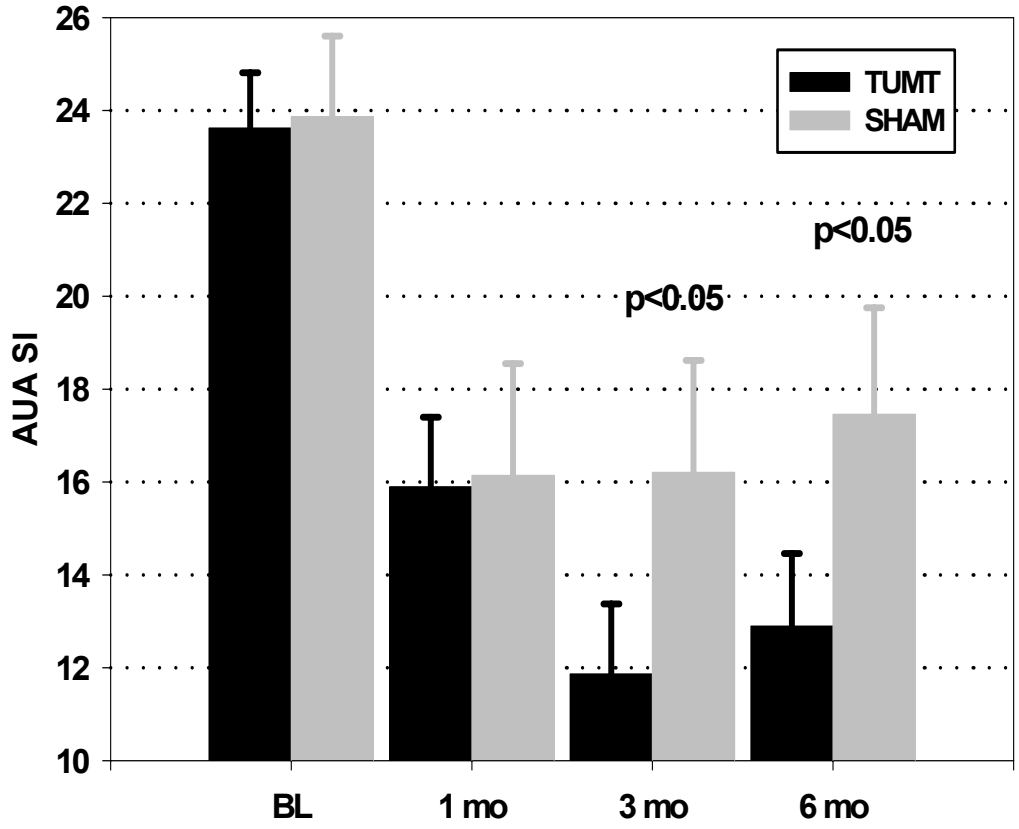

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Figure 3: TUMT versus Sham: Cumulative Frequencies of IPSS Changes

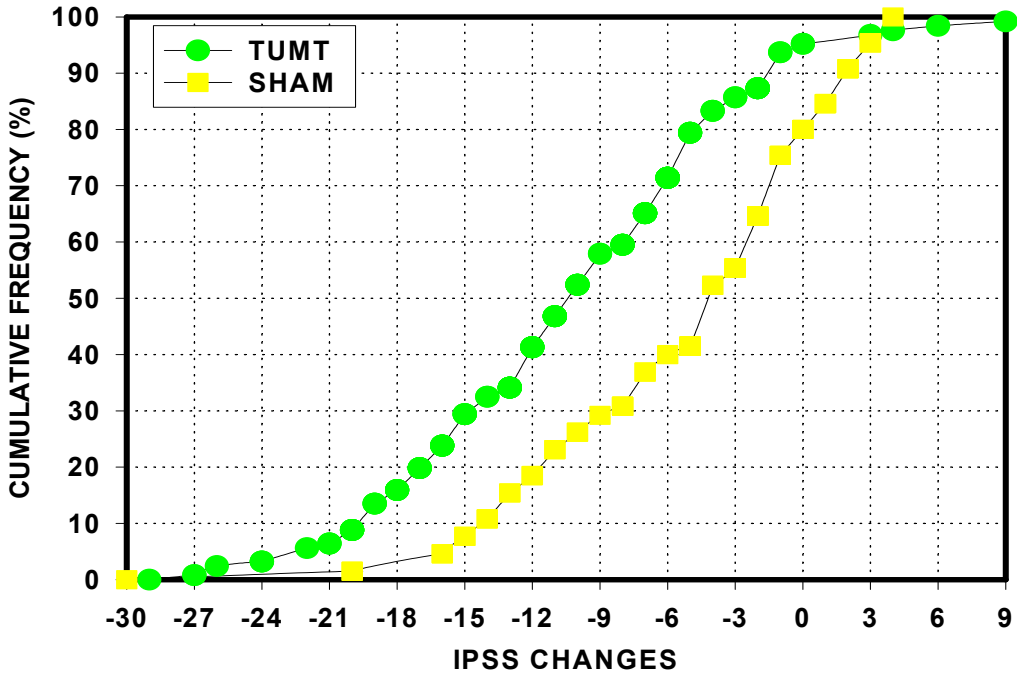

Figure 4: TUMT versus Sham: Cumulative Frequency of IPSS Percent Changes