# Evaluation of Sexual Dysfunction in LUTS/BPH patients

# Dissertation submitted to THE TAMILNADU Dr. M. G. R. MEDICAL UNIVERSITY In partial fulfillment of the

regulations for the award of the degree of

# MCh (UROLOGY) BRANCH-IV



# THE TAMIL NADU DR. MGR. MEDICAL UNIVERSITY CHENNAI, INDIA

**AUGUST 2008** 

#### DECLARATION

I solemnly declare that this dissertation "Evaluation of sexual dysfunction in LUTS/BPH patients" was prepared by me in the Department of Urology, Government Madras Medical College and Hospital, Chennai under the guidance and supervision of Prof. **R.JEYARAMAN, M.Ch.**, Professor &Head of the Department, Department of Urology, Government Madras Medical College, Chennai. This dissertation is submitted to the Tamil Nadu Dr. MGR Medical University, Chennai in partial fulfillment of the University requirements for the award of degree of M.Ch., Genitourinary surgery.

Place : Chennai Date :

#### CERTIFICATE

This is to certify that this dissertation entitled "Evaluation of sexual dysfunction in LUTS/BPH patients" is a bonafide record of the research work done by Dr.Narayanamoorthy. N, for the award of M.Ch., Genitourinary surgery, under the supervision of Prof. R.JEYARAMAN. M.S., M.Ch., Professor & HOD, Dept. Of Urology, Government Madras Medical College, Chennai. I also certify that this dissertation is the result of the independent work done by the candidate.

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#### ACKNOWLEDGEMENT

I am very grateful to my teacher and guide **Prof. R. Jeyaraman**, **Professor & HOD, Urology,** Madras Medical College, Chennai for his expert guidance and help without which this study would not have been possible.

I sincerely thank **Prof. V.Kamaraj, Prof. RM. Meyyappan,** Additional Professors of Urology, Madras Medical College, Chennai who gave me encouragement and moral support for the completion of this study.

I thank all the Assistant Professors of the Department of Urology, Madras Medical College, Chennai, for their encouragement.

I wish to express my sincere thanks to co-postgraduates, patients and all technical staff of Department of urology, for their kind co-operation.

I am thankful to the Dean, Government Madras Medical College and Hospital, Chennai for permitting me to carry out this study at Government Madras Medical College Hospital, Chennai.

#### **INTRODUCTION**

Sexual dysfunction affects a couple's relationship and the quality of life of the patient and the partner irrespective of age. Lower Urinary Tract Symptoms suggestive of BPH is highly prevalent among the elderly. So too are the symptoms of sexual dysfunction in old age. But the symptoms of sexual dysfunction are not concentrated upon, both by the patient and the physician at least in our country. Sexual dysfunction manifests mainly as erectile dysfunction (ED), ejaculatory disorders, or decreased libido/hypoactive sexual desire (HSD). Men with moderate-tosevere LUTS are at increased risk for sexual dysfunction. Though reduced rigidity and reduced ejaculate volume are the highly prevalent symptoms in ageing men, reduced rigidity and pain on ejaculation are considered to be most bothersome, affecting the quality of life.

Sexual dysfunction is much more prevalent in patients with LUTS/BPH than in men without them, even after controlling for confounding variables such as age and co morbid illnesses. Hence LUTS/BPH is considered to be an independent risk factor for sexual dysfunction. <sup>3</sup> The reason for the association being a common underlying pathology or the psychological effect of LUTS / BPH on sexual function needs to be confirmed. Despite a decline in the frequency of sexual intercourse, as well as in overall sexual functioning, most elderly men report regular sexual activity and consider their sex life as an important dimension of their quality of life (QoL). However, most patients with LUTS/BPH experience a negative effect of LUTS on their sex life.

Hence, treatment of LUTS/BPH should also aim to at least maintain or, if possible, improve sexual function.<sup>2</sup>

The successful management of patients with LUTS associated with BPH should include assessments of sexual function and monitoring of medication-related sexual side effects. For men with LUTS and sexual dysfunction, an appropriate integrated management approach, based on each patient's symptoms and outcome objectives, is warranted.<sup>1</sup>

We intended to evaluate the prevalence of sexual dysfunction in the LUTS/BPH patient population in our country, in our set-up to analyze the amount of importance attached to the sexual quality of life and also to see the correlation between LUTS and sexual dysfunction.

### **AIM & OBJECTIVES**

To evaluate the prevalence of sexual dysfunction in LUTS/BPH patients.

To assess the effect of LUTS/BPH effect on sexual function.

To assess the treatment effect of LUTS/BPH on sexual function.

#### **REVIEW OF LITERATURE**

#### **Prevalence of BPH / LUTS**

From the historic times, symptoms of LUT were considered to be part and parcel of normal aging process. The definite relation between aging and LUTS was not evaluated clearly till 1984. In 1984 metaanalysis by Berry and colleagues summarized the data from five studies demonstrating that no men younger than 30 had evidence of BPH and the prevalence rose with each age group, peaking at 88% in men in their 80s. The prevalence increases rapidly in the fourth decade of life, reaching nearly 100% in the ninth decade. It is striking that the age-specific autopsy prevalence is remarkably similar in all populations studied regardless of ethnic and geographic origin

#### **Clinical Prevalence**

The definition of BPH, has undergone several changes in the past decade, and, at present, no single criterion can be applied. In the past, the term "prostatism" was used, incorrectly referring to the prostate as the sole source of the typical LUTS found in aging men. It has been pointed out that there are at least three interrelated phenomena that can be assessed independently, namely the symptoms (formerly called prostatism), enlargement of the prostate gland, and presence of obstruction. In a given patient, all three, two of the three, or only one of the three entities might be present. Paul Abrams coined the term lower urinary tract symptoms to replace the old and inappropriate term prostatism <sup>4</sup>. When evaluating elderly men, one can therefore stratify them by the level of LUTS into mildly, moderately, and severely symptomatic according to a standardized symptom severity and frequency questionnaire <sup>5</sup>. The same patients then can be further classified based on the degree of prostatic enlargement as measured by digital rectal examination (DRE), transrectal ultrasonography (TRUS), or magnetic resonance imaging (MRI) and finally by the presence and degree of bladder outlet obstruction as measured by flow rate recordings or invasive pressure flow studies.

Of all men older than 40, a certain proportion develop histologic hyperplasia of the prostate, that is, BPH. Of those, some but not all develop LUTS, and other may have LUTS for reasons other than BPH (e.g., urethral stricture, stones, inflammation). Prostate enlargement occurs in some but again not all men with histologic BPH and LUTS, and some men with enlarged glands may not have any symptoms at all. Urodynamically proven obstruction may be present in all the combination groups of men who have one, several, or all of histologic BPH, LUTS, and enlarged glands, yet others may have obstruction without having any evidence of BPH (e.g., urethral stricture, prostate cancer, primary bladder neck sclerosis). In addition to the mere enumeration of symptoms by frequency of occurrence, the bother associated with the symptoms, interference with activities of daily living, and the impact of the symptoms on quality of life are important distinguishing characteristics. When studying the prevalence of clinical BPH—admittedly an imprecise term describing the constellation of LUTS, bother, interference, quality of life impact, with or without enlargement, obstruction, and so forth—disease definitions may be applied that take either one or several of these items into consideration. Thus, rather than describing truly the prevalence of a disease in populations, one can describe the distribution of certain attributes of such disease in different populations stratified by age.

#### **Symptom Severity and Frequency**

The development, validation, and translation with cultural and linguistic validation of the standardized, self-administered seven-item American Urological Association (AUA) symptom index (also known as the International Prostate Symptom Score [I-PSS]) has been a pivotal event in the clinical research on LUTS and BPH <sup>5</sup>. With the total score running from 0 to 35 points, patients scoring 0 to 7 points are classified as mildly symptomatic, those scoring from 8 to 19 points as moderately symptomatic, and those scoring 20 to 35 points as severely symptomatic.

This instrument is an integral part of virtually every epidemiologic study as well as treatment studies in the field, and the availability of validated translations in many common languages allow cross-cultural comparisons of unprecedented scope. Socioeconomic factors do not seem to influence responses to the questionnaire, and fundamentally similar responses are obtained when the questionnaire is self-administered, read to the patient, mailed in, or administered in some other way <sup>6</sup>. However, there is no question that subtle differences in comprehension of the translated questionnaire as well as different perception of the symptoms, willingness to admit to the symptoms, and other factors are the cause for cross-cultural differences in symptom severity reported in the literature.

A very large international investigation of LUTS in Asian men was undertaken by Homma and colleagues (1997) in which 7588 men from Japan, China, Taiwan, Korea, the Philippines, Thailand, Singapore, Pakistan, India, and Australia were queried. The finding of 18%, 29%, 40%, and 56% of men in their 40s, 50s, 60s, and 70s having moderate to severe symptoms was in line with the other studies reported both from Asia and from Europe and North America. In addition to the major community-based studies listed, other studies have been published with similar findings but often done under less stringent conditions. Despite the significantly different proportion of men admitting to moderate to severe symptoms, a clear trend toward an increase in symptom scores with advancing age is noticeable in all reported studies.

#### Prevalence of sexual dysfunction in aging men & LUTS patients

The results of several recent large-scale studies have shown a consistent and strong relationship between LUTS and both ED and EjD. It appears that the pathophysiological mechanisms of LUTS and the

related prostatic enlargement of BPH as well as certain treatments for this condition may have an impact on both the erection and ejaculation components of the sexual response.

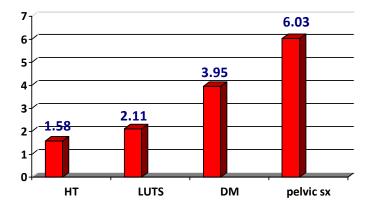
#### **Epidemiological studies**

#### MMAS (Massachusetts Male Aging Study)

The MMAS was a community based, random sample observational survey of men 40 to 70yrs old conducted from 1987-1989 in Boston MA. A self administered sexual activity questionnaire was used to assess the erectile potency<sup>7</sup>. The MMAS documented that ED is a highly prevalent disorder that frequently coexists with other risk factors, both medical and psychosocial. The 8 year longitudinal survey that followed MMAS clearly showed that ED increases with age.

#### **Cologne Male Survey**

The Cologne Male Survey was conducted in a similar fashion. In this study instead of considering the percentage of incidence, odds ratio was calculated <sup>8</sup>. The study showed LUTS have a risk ratio of 2.11 in patients with ED.

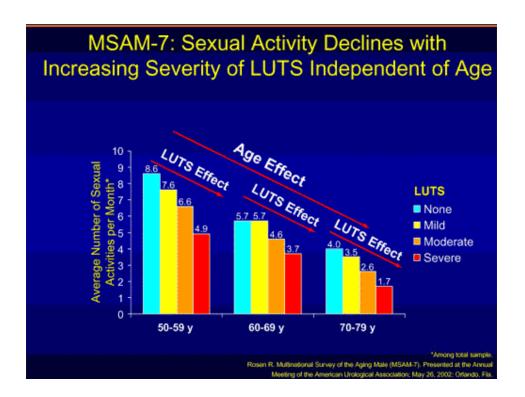


The Multinational Survey of the Aging Male (MSAM-7)

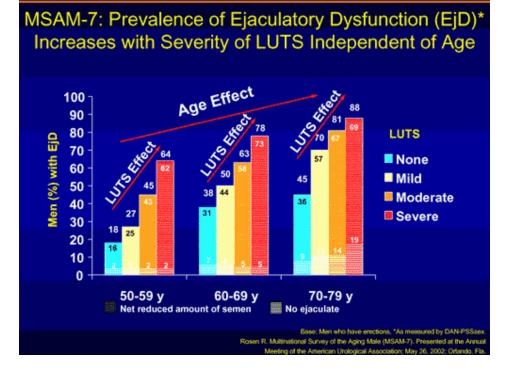
The Multinational Survey of the Aging Male (MSAM-7) was conducted in the United States and 6 European countries in 12,815 men aged 50-80 years. It investigated the relationship between LUTS and sexual dysfunction in aging men by mailed questionnaiirre. International Prostate Symptom Score, the Danish Prostatic Symptom Score, and the International Index of Erectile Function and a health and demographics questionnaire were used.

The results were consistent from one country to another. Sexual activity was reported by 83% of the sample, with 71% reporting at least one episode of sexual activity during the previous 4 weeks. Sexual disorders and their bother were strongly related to both age and severity of LUTS. The relationship between sexual problems and LUTS is independent of co-morbidities such as diabetes, hypertension, cardiac disease, and hypercholesterolemia. The major finding was that LUTS

severity is a major risk factor for sexual dysfunction (both erection and ejaculation problems) independent of other risk factors (Figures 1 and 2).



**Figure 1.** Multinational Survey of the Aging Male-7: sexual activity declines with increasing severity of lower urinary tract symptoms independent of age.



# **Figure 2.** Multinational Survey of the Aging Male-7: prevalence of ejaculatory dysfunction (EjD) increases with severity of lower urinary tract symptoms independent of age

With these results it was concluded that Sexual activity is common in a majority of men over age 50 and is an important component of overall quality of life. The presence and severity of LUTS are independent risk factors for sexual dysfunction in older men.

#### **Epidemiological studies summary**

It appears from epidemiological data that there is a global correlation between LUTS and erectile dysfunction. Little evidence supporting the connection was available until the mid-1990s, when several epidemiological studies assessing the prevalence of BPH and associated quality-of-life issues suggested that LUTS by themselves could affect sexual function. Later, many authors reported an association between LUTS and various aspects of sexual dysfunction. The link between LUTS and sexual dysfunction was unambiguously confirmed by the Multi-National Survey of the Ageing Male-7. Hence, epidemiological studies provide clear evidence that LUTS and sexual dysfunction, including ED and abnormal ejaculation, are strongly linked. However, a causal relationship between LUTS and sexual dysfunction cannot be established based on these data alone, as the underlying pathophysiological mechanisms need to be determined.

#### Potential causes of sexual dysfunction;

The underlying mechanism may be physiological, pathophysiological or psychological.

#### **Erectile dysfunction;**

The causal relationship between ED and LUTS can be explored using Hill's causality method, which separates causal from non-causal explanations. This establishes a link using general epidemiological data, case-control reports, and cohort studies grounded by a supportive plausible mechanism of action. The epidemiological data are examined for the strength of association (relative risk), consistency (replication of findings), dose–response effect and temporal relationship (effect of onset or cessation of LUTS on ED and vice versa). Moreover, even if there is a link between ED and LUTS from an epidemiological perspective, then the causal relationship must be shown to have biological plausibility before any widespread acceptance is possible. Four theories supporting biological plausibility currently exist <sup>10</sup>.

#### The NOS/NO theory

This hypothesis attempts to explain the link between ED and LUTS by the reduced production of NOS/NO in the pelvis, which includes the penis, bladder and prostate. NO is a multifunctional molecule originally described as a vasodilator. The NOS/NO theory suggests that reduced NOS/NO results in smooth muscle cell proliferation, which may result in structural changes in the prostate and simultaneous increased contraction which affects outlet resistance and bladder compliance, leading to LUTS.<sup>11</sup>

#### Autonomic hyperactivity and metabolic syndrome

It was also proposed that LUTS secondary to BPH is a part of the metabolic syndrome, which includes glucose intolerance, insulin resistance, obesity, dyslipidaemia and hypertension, all known risk factors for ED<sup>12,13</sup>. Manipulation of the autonomic innervation of the pelvis has a profound effect on prostate growth and differentiation <sup>14</sup>. Increased autonomic nervous system activity has been shown to induce BPH in ageing rats, and ED <sup>15</sup>. Concordant evidence also comes from observations in spontaneously hypertensive rats that develop autonomic

hyperactivity, prostate hyperplasia and ED, and have increased voiding frequency and detrusor overactivity<sup>16</sup>. Altered responses to corpus cavernosum nerve stimulation and smooth muscle contraction in these rats correlate with ED<sup>17</sup>.

In humans, autonomic nervous system hyperactivity is also associated with signs and symptoms of LUTS secondary to BPH. McVary *et al.* <sup>18</sup> as part of the MTOPS study, evaluated the autonomic nervous system activity in 38 men before enrolment. Tilt-table testing (a measure of autonomic tone and reactivity) revealed that increased sympathetic tone (as measured by changes in blood pressure, heart rate, urinary and serum catecholamine levels) was significantly associated with the level of LUTS even when controlled for cofactors known to influence the sympathetic tone (age, body mass index, abdominal obesity, Cpeptide and insulin levels, physical inactivity). Further analyses showed that autonomic hyperactivity was strongly related to the total IPSS, the BPH Impact Index and the bother score (IPSS question 8) and to a lesser extent to the total prostate volume and transitional zone volume.

#### Increased Rho-kinase activation/endothelin activity

Smooth muscle contraction has been attributed to an increase in the intracellular calcium concentration. The Rho-kinase pathway is likely to regulate smooth muscle tone in conditions in which tonic contraction or high basal tone is involved <sup>19</sup>. Increased Rho-kinase activity, and consequently increased calcium sensitivity of the contractile machinery,

can be found in the detrusor or corpus cavernosum of rabbits with partial BOO or diabetes, and in vascular smooth muscle in hypertension. The actions of several factors beside noradrenaline (e.g. endothelin-1, angiotensin II), possibly involved in the increased smooth muscle activity found in both LUTS/BPH and sexual dysfunction, are dependent on Rho-kinase activity that acts downstream from these receptors <sup>20</sup>. It is therefore tempting to speculate that the common link between LUTS and sexual dysfunction is increased Rho-kinase activity.

#### **Pelvic atherosclerosis**

There is a high prevalence of vascular risk factors (hypertension, diabetes, hypercholesterolaemia, smoking) in elderly men, suggesting the possible involvement of atherosclerosis in the aetiology of BPH. Chronic ischaemia is associated with an increased production of TGF- $\beta$ 1 that correlates with the severity of fibrosis. It also impairs neurogenic relaxation in the prostate, which appears to involve the NO pathway, and may result in a loss of elasticity and increase in smooth muscle tone of the prostate <sup>21</sup>.

#### Post treatment effect

Although surgery, minimally invasive therapies, and pharmacologic therapies can all improve LUTS and the peak urinary flow rate, some can cause or exacerbate ED (incidence rates: surgery, 10%; minimally invasive therapies, 1%–3%; pharmacologic monotherapy or

combination therapy, 3%-10%) and EjD (incidence rates: surgery, 65%; minimally invasive therapies, 4%-16%; pharmacologic monotherapy or combination therapy, 0%-10%)<sup>22</sup>.

## Impact of medical therapies for BPH on sexual function

#### **5α-reductase inhibitors**

The  $5\alpha$ -reductase inhibitors (finasteride, dutasteride) act by inhibiting the conversion of testosterone to  $5\alpha$ -dihydrotestosterone (DHT). They are recommended for treating LUTS in men with large prostates. There is evidence from randomized controlled trials and metaanalyses that finasteride and dutasteride are equally effective in reducing prostatic size, serum PSA level and serious outcomes such as acute urinary retention and the need for BPH-related surgery. Side-effects of  $5\alpha$ -reductase inhibitors are related to sexual function and include decreased libido, erectile dysfunction (ED and ejaculatory dysfunction (EjD) <sup>23,24,25</sup>. Gynaecomastia is also more frequent than with placebo. Hence, in a recent meta-analysis by the AUA, finasteride, an inhibitor of the type II  $5\alpha$ -reductase isoenzyme, was associated with a greater incidence of ED (8%), decreased libido (5%) and EjD (4%) than with placebo (4%, 3% and 1%, respectively). The sexual side-effect profile of dutasteride, a novel inhibitor of both type I and type II  $5\alpha$ -reductase isoenzymes appears closely similar to that of finasteride. In a pooled analysis of three double-blind placebo-controlled studies which included 4325 men aged  $\geq$  50 years and with BPH, dutasteride administered for

2 years was associated with a significantly higher incidence of ED (7.3%), decreased libido (4.2%), gynaecomastia (2.3%) and EjD (2.2%) than was placebo (4.0%, 2.1%, 0.7% and 0.8%, respectively). Moreover, in a direct comparative study of 1-year duration which included 1630 patients with LUTS, dutasteride and finasteride showed comparable incidences of ED (7% vs 8%, respectively), decreased libido (5% vs 6%), EjD (1% vs 1%) and gynaecomastia (1% vs 1%)

The pathophysiology of increased sexual dysfunction with  $5\alpha$ -reductase inhibitors is not known precisely, but might be related to the reduction in DHT.

#### a1-adrenergic blockers

It is well established that all  $\alpha_1$ -adrenoceptor blockers currently recommended for treating LUTS (alfuzosin, doxazosin, tamsulosin, terazosin) have an equal clinical effectiveness, producing a mean 4– 6 point improvement in the IPSS <sup>23</sup>. However, they differ in their sideeffect profile. In the AUA meta-analysis, while the four  $\alpha_1$ -adrenoceptor blockers showed incidences of decreased libido (1–3%) and ED (3–5%) closely similar to placebo (3% and 4%, respectively), tamsulosin was associated with a higher incidence of EjD (10%) than the other  $\alpha_1$ adrenoceptor blockers (0–1%) and placebo (1%). The higher incidence of EjD, based of patients' spontaneous reports in clinical trials, is doserelated. Hence, in a 3-month placebo-controlled study conducted in the USA, the incidence of abnormal ejaculation with tamsulosin increased from 6% with the 0.4 mg dose to 18% with the 0.8 mg dose, while no patient receiving placebo reported EjD. The incidence of EjD while on tamsulosin may also increase over time, as shown in long-term extensions of phase III clinical studies. Over a 53-week treatment period, abnormal ejaculation was reported by 10% and 26% of patients with the 0.4 mg and 0.8 mg doses of tamsulosin, respectively. Over a mean duration of treatment of 64.5 weeks, 30% of patients treated with tamsulosin (0.4–0.8 mg per day) reported abnormal ejaculation.

To try to elucidate the pathophysiological mechanism of EjD associated with  $\alpha$ 1-adrenoceptor blockers, a double-blind, placebocontrolled, crossover study (ABnormal EJACulation with alfuzosin and tamsulosin, ABEJAC) compared the effects on ejaculation of placebo, alfuzosin 10 mg once daily and tamsulosin 0.8 mg once daily in 48 healthy volunteers aged 18–36 years, and having a normal sexual function documented by the International Index of Erectile Function<sup>26</sup>. The trial was divided into three treatment periods, so each subject received each treatment once (placebo, alfuzosin and tamsulosin) for 5 days, with each treatment period separated by a 10-day washout period. The 0.8 mg dose of tamsulosin was chosen to ensure an evaluable incidence of EjD, in this first mechanistic study ever conducted on such a topic. The primary endpoints of the study were the amount of ejaculate volume after masturbation (and after abstaining from sexual activity for  $\geq$ 48 h), and sperm concentration in the urine after ejaculation. The mean (sd) ejaculate volume at baseline was 3.4 (1.4) mL. Tamsulosin markedly decreased the ejaculate volume, by -2.4 (0.17) mL, compared to alfuzosin, at + 0.3 (0.18) mL (P < 0.001 vs tamsulosin) and placebo, at + 0.4 (0.18) mL (P < 0.001 vs tamsulosin; not significant vs alfuzosin). There was a decrease in ejaculate volume of >20% in 90% of subjects during tamsulosin treatment, compared to 21% with alfuzosin (P < 0.001vs tamsulosin) and 12.5% with placebo (P < 0.001 vs tamsulosin, not significant vs alfuzosin). Moreover, 35% of subjects had no ejaculation with tamsulosin, compared to none while on alfuzosin or placebo. This reduced or absent ejaculation was not due to retrograde ejaculation, as confirmed by the absence of an increased sperm count in urine samples (changes in urine sperm concentration,  $10^6$ /mL, were + 1.4 with placebo, + 1.2 with alfuzosin, and + 1.7 with tamsulosin; between group p = ns

The ABEJAC study thus confirmed that a functioning bladder neck has no role in the different effects of alfuzosin and tamsulosin on ejaculatory function. Similar conclusions were drawn from a pilot study conducted in 17 Japanese healthy male urologists <sup>27</sup>. They received, in a crossover protocol, tamsulosin 0.2 mg and 0.4 mg once daily over 3 days, followed by measurements of the amount of ejaculate and sperm concentration in midstream urine samples after ejaculation, each ejaculate being obtained after 3 days of abstinence. The amount of ejaculate was significantly lower with both doses of tamsulosin, at 1.75 (1.3) mL with the 0.2 mg dose and 1.64 (1.6) mL with the 0.4 mg dose, compared to controls, at 3.21 (1.2) mL. There was a reduction in ejaculation volume of >80% from baseline in a third of the volunteers. There was no sperm in midstream urine samples after ejaculation in any of the volunteers before or after tamsulosin, confirming that the objective reduction in ejaculate volume was not due to retrograde ejaculation.

There is thus evidence that tamsulosin causes dose-dependent reduction in the amount of ejaculate and that it starts objectively from the 0.2 mg dose. The underlying mechanism is not retrograde ejaculation. Several additional hypotheses have been postulated.

#### Mechanisms of impaired ejaculation with Tamsulosin

The ejaculation process includes two distinct phases: (i) The *emission phase* involves secretion of seminal fluids from the accessory sex glands and contraction of the seminal tract from the epididymis to the prostate. This is associated with a strong closure of the bladder neck as soon as the emission starts, to prevent retrograde ejaculation; (ii) The *expulsion phase* involves rhythmic contractions of the striated perineal muscles (particularly the bulbospongiosus smooth muscle) with involvement of the urethral smooth musculature, which expel the semen from the prostatic urethra to the urethral meatus. Two different hypotheses, peripheral and central, have been currently suggested to explain the observed impairment of ejaculation with tamsulosin.

#### **Peripheral hypothesis**

 $\alpha_{1A}$ -adrenoceptors are widely distributed in all the organs participating in the emission phase (epididymis, vas deferens, seminal vesicle, prostate gland, prostatic urethra and bladder neck). This means that  $\alpha_{1A}$ -adrenoceptors play a role in the emission phase of ejaculation. Tamsulosin, which is the only  $\alpha_1$ -adrenoceptor blocker showing some  $\alpha_{1A}$ selectivity, may affect this first phase of ejaculation.

In a study , increased seminal vesicle pressure, mimicking the emission phase of ejaculation, was induced in anaesthetized Wistar rats by electrical stimulation of the hypogastric nerve, before and after an i.v. injection with vehicle or tamsulosin (3 and 10  $\mu$ g/kg) or alfuzosin (3 and 10  $\mu$ g/kg). Both doses of tamsulosin significantly decreased the contraction of the seminal vesicle, while both doses of alfuzosin had only marginal effects on it. Because the seminal vesicle is the major contributor to the volume of semen, such an effect of tamsulosin is likely to reduce significantly the amount of ejaculate volume. A limitation of the study was that the dose levels used (identical for both drugs) may not have appropriately reflected those used in clinical practice <sup>28</sup>.

In another study, the effects of alfuzosin  $(10 \ \mu g/kg, i.v)$  and tamsulosin  $(3 \ \mu g/kg, i.v)$  were tested on the contractions of the epididymal and prostatic portions of the rat vas deferens, induced either by noradrenaline or by nerve stimulation. Tamsulosin and alfuzosin

significantly differed in their effects on epididymal and prostatic portions of the vas deferens, i.e. tamsulosin was associated with an abnormal increase in the contractions of prostatic portions of the vas deferens, which is likely to alter the progression and emission of sperm. There was no such effect with alfuzosin.

#### **Central hypothesis**

Both the brain and spinal cord are crucial in triggering the emission and expulsion phases of ejaculation. Electrical recordings from the bulbospongiosus muscle contractions occurring during expulsion in humans showed that electrical activity during ejaculation is highly organized <sup>29</sup>. Delivery of 8-OH-DPAT, a 5HT<sub>1A</sub> and D<sub>2</sub>-like agonist, to the brain of anaesthetized male rats produces organized electrical activity in the bulbospongiosus muscle, mimicking what happens during the expulsion phase of ejaculation <sup>30</sup>.

This can therefore be used as an experimental model to investigate the central control of ejaculation. A central effect is therefore plausible, as tamsulosin has a strong affinity for  $5HT_{1A}$  and  $D_2$ -like receptors, both of which are involved in the central control of ejaculation.

	Median % (95% CI) problems with			
Therapy	Ejaculation	Erection	Libido	
α-blockers				
Alfuzosin	_	3 (1-6)	1 (0-4)	
Doxazosin	0 (0–2)	4 (1-8)	3 (2–6)	
Tamsulosin	10 (6–15)	4 (1-8)		
Terazosin	1 (1–2)	5 (3-8)	3 (1–5)	
Hormonal				
Finasteride	4 (3–5)	8 (6–11)	5 (4–7)	
Combined				
Alfuzosin/finasteride	1 (0–2)	8 (5–11)	2 (1-4)	
Doxazosin/finasteride	3 (2–6)	10 (7–14)	3 (1–5)	
Terazosin/finasteride	7 (5–10)	9 (1–13)	5 (3-8)	
Placebo	1 (1–1)	4 (3–5)	3 (3–4)	

AUA meta-analysis of outcomes of medical therapies: estimates of occurrence of sexual adverse events - Adapted from (31)

#### Minimally invasive therapy

The effects of open prostatectomy, transurethral resection, transurethral vaporization, doxazosin and finasteride on sexual functions of men were investigated in a total of 305 patients with benign prostatic hyperplasia. The sexual functions of the patients were assessed with a questionnaire before treatment and 3 and 6 months after the treatment. A total of 212 (70%) patients were judged to be potent before the treatment. At 3 months, open prostatectomy and transurethral resection caused erectile dysfunction in 2 of 40 (5%) and 5 of 89 (6%) potent patients, respectively. At 6 months, one of the patients from the former and 2 of

the patients from the latter groups who developed erectile dysfunction at 3 months stated improvement. Transurethral vaporization caused loss of erectile functions in 4 of 14 potent patients (29%) at the 3-month followup and, one of these patients recovered erectile functions at 6 months. Only one of the 33 patients (3%) using doxazosin stated that he lost his erectile functions both at 3 months and 6 months. At 3 months follow-up, finasteride caused loss of erectile functions in 8 of 36 potent patients (22%). Four of these patients underwent surgery (transurethral resection) after 3 months of finasteride use. At the 6-month follow-up, 4 more patients suffered from loss of erectile functions <sup>32.</sup>

The mean probability of a patient becoming impotent following a transurethral resection of the prostate (TURP) would be approximately 13.6% with a 90% confidence interval of 3.4% to 32.4%. This needs to be considered in the context of a 4.3% erectile dysfunction rate following an unrelated general surgical procedure, undoubtedly attributable to a "sham" effect. The *AHCPR Guideline* suggested that further research was needed to determine the "number of patients who subsequently developed impotence, ejaculatory dysfunction, incontinence, and drug-related side effects" following treatment.<sup>33</sup>

The belief that TURP could be responsible for erectile dysfunction based on relatively poor evidence from uncontrolled studies published prior to 1994 was shattered in 1995 by the publication of data from a VA Cooperative Study comparing the outcomes of TURP and watchful waiting in 556 men with moderate LUTS. In this study, TURP was not associated with changes in either general well-being, social activities, or sexual performance (P=0.92). In fact, at the end of the 3-year study, 19% of patients in the surgery group and 21% of those in the watchful waiting group reported that their sexual performance was worse, while 3% in each group reported it was improved. In general, the spouses or partners thought that the patients' sexual performance was unaffected over the course of the study <sup>34</sup>.

#### **Sexual Function Following High Energy Microwave Thermotherapy**

In a study<sup>35</sup>, 147 patients were randomized to either undergo TURP or transurethral microwave thermotherapy (TUMT) using a high energy protocol. Patients were given a self-administered questionnaire before the treatment and 3 and 12 months after the treatment. While LUTS improved in both treatment groups, the magnitude of the improvement was clearly greater in the TURP group compared with the TUMT group. However, at 3 months, only 27% of the TURP group had ante grade ejaculation compared with 74% of the TUMT group. These numbers were unchanged at the 1-year follow-up point. One can therefore state that approximately two-thirds of men will suffer retrograde ejaculation following TURP versus only one-third of men following high energy microwave thermotherapy. Changes in sexual function were experienced in 36% of patients undergoing TURP versus 17% undergoing TUMT. Patients were asked regarding their overall satisfaction with sexual function, and it was noted that, in the TUMT group, 76% were either very satisfied or satisfied prior to treatment versus 81% after 3 months. In the TURP group, 69% were either very satisfied or satisfied before treatment versus 85% following treatment. Problems with erection were reported in 20% of the TUMT and 17% of the TURP-treated patients.

#### **Evaluation of sexual function or dysfunction**

#### **Questionnaires and Sexual Function Symptom Scores**

Many male sexual function profiles and ED questionnaires have been developed. Formerly, the aim of these detailed questionnaires was to differentiate psychogenic from nonpsychogenic ED. More recently, a variety of self-report measures for assessing the levels of male sexual function or dysfunction have been described; self-administered questionnaires (SAQs) have seen their greatest use in clinical trials. SAQs provide quantifiable efficacy endpoints for new drug trials; they attempt to quantify sexual interest, performance, and satisfaction. Those most commonly referred include the International Index of Erectile Function (IIEF) <sup>36</sup>, Brief Male Sexual Function Inventory (BMSFI), Dysfunction Inventory for Treatment Satisfaction (EDITS). Other self-report measures include the Derogatis Sexual Function Inventory (245 items), the Center for Marital and Sexual Health Questionnaire (18 items), and the recently added Male Sexual Function Scale (Rosen R) <sup>37</sup>. The BMSFI instrument covers sexual drive (2 items), erection (3 items), ejaculation (2 items), perceptions of problems in each area (3 items), and overall satisfaction (1 item). The EDITS questionnaire is very useful in drug studies; Ultimately, in the clinic, satisfaction rates are established by prescription refills, dropouts, and requests for further evaluation

The IIEF is the most widely used SAQ, and it is statistically validated in many languages. Its 15 items address and quantify five domains: erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction.

In the hope of providing physicians with a "checklist" on erectile function that could be used in an office setting, an abridged 5-item version of the IIEF-15 has been developed <sup>38</sup>, in which 4 items are taken from the erectile function domain. The fifth item addresses sexual intercourse satisfaction; it was chosen to reflect the central element in the NIH Consensus Panel (1992) definition of ED, which ties erectile function to satisfaction: "maintain erection of sufficient rigidity and duration to permit satisfactory sexual performance." Perhaps the most important difference between the IIEF-15 and the IIEF-5 is that the latter asks patients to self-assess erectile function and satisfaction over the past 6 months, a more clinically relevant and practical time frame than 4 weeks. ED severity is classified into five categories based on the IIEF-5: severe (5 to 7), moderate (8 to 11), mild to moderate (12 to 16), mild (17 to 21), and no ED (22 to 25).

The Male Sexual Function Scale was developed in conjunction with the Second International Consultation on Sexual Dysfunction is based on qualitative research in normal and sexually dysfunctional men and assesses core components of male sexual function (desire, erection, ejaculation, satisfaction) in both clinical and research settings. The scale was designed by an independent advisory board of experts in male sexuality, without involvement or funding from industry. This new screening tool is suitable for use in both primary care and urology practice settings and may be valuable in screening patients for sexual dysfunction after pelvic surgery or with chronic illness or medications

One major drawback of sexual inventories is their reliance on selfassessment. Blander and coworkers (1999) have demonstrated that SAQs do not differentiate among the various causes of ED (arterial, venous, or mixed vascular), and evidence-based assessments (diagnostic tests) are still necessary in patients with complex ED.

#### **Treating patients with ED and BPH/LUTS**

#### α<sub>1</sub>-Adrenergic blockers and ED

Selective  $\alpha_1$ -adrenergic blockers relax smooth muscle cells in the bladder neck, prostatic urethra and prostatic stroma . Alfuzosin,

doxazosin, tamsulosin and terazosin are all considered appropriate  $\alpha_1$ adrenergic blockers for treating LUTS suggestive of BPH <sup>39</sup>. They do not affect libido or erectile function, and could even have, in some cases, a positive effect on ED

#### **Clinical studies**

Sexual dysfunction is a concern in hypertensive patients because antihypertensive medication is an important risk factor for ED. The Treatment of Mild Hypertension Study (TOMHS) examined the effects of various antihypertensive agents on sexual function <sup>40</sup>. Overall, 902 patients (557 men and 345 women) aged 45-69 years with stage 1 diastolic hypertension were randomized to receive placebo or one of five active drugs (acebutolol, amlodipine, chlorthalidone, doxazosin, enalapril) over 48 months. At baseline, 14.4% of men reported ED problems. The incidences of ED during the follow-up were 9.5% and 14.7% at 24 and 48 months, respectively, and were related to the type of antihypertensive treatment. When compared with other active treatments, the incidence of ED was lowest in the doxazosin group, although the difference vs placebo was not statistically significant. In addition, disappearance of erection problems among men with problems at baseline was greatest for men treated with doxazosin.

Another  $\alpha_1$ -adrenergic blocker, alfuzosin 10 mg once daily, administered for 1 year in 3076 men with LUTS suggestive of BPH, also

gave significant improvements from baseline in both ED and EjD (reduced ejaculation and painful ejaculation) assessed by the DAN-PSSsex These improvements were particularly marked in men with severe LUTS or severe bother at enrolment. Moreover, alfuzosin 10 mg once daily administered for 2 years in 799 men with LUTS also significantly improved from baseline all domains of the Brief Sexual Function Inventory (BSFI), including sexual drive (P < 0.05), erectile function (P < 0.05), ejaculation (P < 0.05), bother associated with sexual problems (P < 0.05) and overall satisfaction with sex life (P < 0.001). Once again, improvements were greater in men with severe LUTS at baseline.

#### Phosphodiesterase-5 (PDE-5) inhibitors and LUTS

#### **Clinical studies**

In a pilot study <sup>41</sup>, 111 patients with ED attending an andrology outpatient clinic were offered oral sildenafil 'on demand' and reviewed after 1 and 3 months of treatment. They completed the IIEF and the IPSS questionnaires at baseline and at each visit after inclusion. At enrolment, 67% of men had mild LUTS, 26% moderate LUTS and 6% severe LUTS. Under sildenafil treatment, both the IPSS and bother score severity improved from baseline. Moreover, men with a lower LUTS or bother score at baseline had higher (i.e. better) IIEF scores after 3 months of treatment. Nitric oxide (NO) and PDE-5 isoenzymes have been identified in the human prostate. The improvement of LUTS with sildenafil might thus be mediated by increased NO activity, resulting in smooth muscle cell relaxation. Placebo-controlled studies are currently ongoing with two different PDE-5 inhibitors, sildenafil and tadalafil, to confirm their possibly beneficial effect in the treatment of LUTS.

# Combined $\alpha_1$ -Adrenergic blockers and PDE-5 inhibitors for treating LUTS and ED

#### **Clinical studies**

Currently, very few studies have evaluated the effect on LUTS and ED of combining an  $\alpha_1$ -adrenergic blocker with a PDE-5 inhibitor. In a retrospective analysis of 42 men with ED, considered nonresponders to tadalafil monotherapy, the addition of an  $\alpha_1$ -adrenergic blocker (alfuzosin 10 mg once daily) to tadalafil (20 mg on demand), improved ED in 71% of patients <sup>42</sup>. The side-effect profile was similar to that of tadalafil monotherapy and there were no significant alterations in blood pressure (BP). The possibly synergistic effect of both medications can be explained by their different mechanisms of action. Alfuzosin, by blocking  $\alpha_1$ -adrenergic receptors and reducing the sympathetic tone in penile smooth muscle and prostate/bladder neck, could enhance the vasoactive influence of tadalafil, that acts through the NO pathway. Here again, placebo-controlled studies are needed to confirm these results.

#### Safety profile

Due to the strong association between LUTS and sexual dysfunction, the co-prescription of drugs treating both LUTS and ED is increasing. As both  $\alpha_1$ -adrenergic blockers and PDE-5 inhibitors can have a slight impact on BP, physicians were concerned about possible haemodynamic interaction between these classes of drugs.

#### **Clinical considerations when treating ED and BPH/LUTS**

Given a common cause, the effective management of ED and BPH/LUTS is a regimen of mutually beneficial agents. However, the safety profile of each drug, especially the effect on the cardiovascular system for  $\alpha_1$ -adrenergic blockers, must be considered in the final choice of drugs to be combined. Doxazosin was associated with a particularly low incidence of ED in men with hypertension (TOHMS) and might have a beneficial effect in patients who failed to respond to agents specifically formulated to improve ED <sup>43</sup>. Thirty-eight men with moderate to severe ED who failed to respond to an intracavernosal injection with alprostadil, a synthetic prostaglandin-E<sub>1</sub> agent, received doxazosin titrated to 4 mg daily over 3 weeks, combined with intracavernosal alprostadil on demand. Overall, 58% of patients had a significant (>60%) improve ED and EjD, as assessed by the DAN-PSSsex and BSFI questionnaires, in men with LUTS, and to improve ED in combination

with tadalafil, in nonresponders to tadalafil monotherapy. Tamsulosin has also been found to have some benefit on sexual quality of life in men with BPH/LUTS, although it can be associated with EjD.  $\alpha_1$ -adrenergic blockers can also be safely used with PDE-5 inhibitors, with which they might act synergistically.

The  $5\alpha$ -reductase inhibitors are used to treat patients with LUTS and prostatic enlargement, and can be associated with ED, low libido, and decreased ejaculatory volume. They can be used concomitantly with PDE-5 inhibitors.

# **MATERIALS & METHODS**

Between June 2007 and November 2007, all patients admitted into our ward with LUTS/BPH were included for evaluation. These patients were admitted for either evaluation or intervention for LUST/ BPH.

- Informed consent obtained from all eligible patients.
- All patients after admission were given the linguistic version of IPSS & MSHQ
- Pts who are literate were asked to fill up the questionnaire. (Self administered questionnaire)
- Pts who were not able to fill up (for various reasons like illiterate, poor eye sight, not able to understand the contents) were interviewed personally.
- To avoid interviewer bias, the same interviewer interviewed all pts.
- All details regarding the pts demographics, scoring, results will be entered into a proforma
- Post treatment effect evaluation was done at the end of 3 months following treatment.

# Initial evaluation;

The patients with complaints suggestive of LUTS/ BPH were thoroughly evaluated with

History & Physical examination,

DRE & Focused neurological examination,

Baseline blood parameters,

USG KUB, Uroflow & PVR.

# **Inclusion criteria**

- All patients with history suggestive of LUTS/BPH with more than 50 years were included.
- 2. Patients who gave informed consent for the study were included.

# **Exclusion criteria**

After the initial evaluation the patients were excluded using the following exclusion criteria.

- 1. Patients who have been already treated for LUTS / BPH earlier.
- 2. Patients with co-morbid illness like DM & HT.

- 3. Patients with history or clinical examination suggestive of associated neurological disorder.
- 4. Patients who were not willing to self-administer the questionnaire or to be interviewed.

#### Symptom severity & Sexual function assessment

All the patients were given with the linguistic version of the International - Prostate Symptom Score (I - PSS).

Sexual function assessment was done using linguistic version of the Male sexual Function Scale. The Male Sexual Function Scale consists a total of 8 questions of which two questions are on erectile function domain & its bother and three are on ejaculatory function domain & its bother, one question each on sexual desire and satisfaction. The final question assessed the overall bother or distraction of life due to the sexual dysfunction.

The linguistic conversion was done by the investigator with the help of a Psychologist who had experience in interviewing such type of patients. At most care was taken in phrasing the words so that it should not be embarrassing to the patient. Before put into use in this clinical study, the questionnaire was circulated among out patients who were waiting for ultrasound examination. They were asked to comment on the content whether it is understandable or not, and their suggestions were taken. The investigator interviewed patients (78 patients – 65%) who are illiterate and who could not read the questionnaire because of poor eyesight and who could not understand the content. To avoid bias, the same investigator interviewed all such patients. In all other patients (42 patients -35%) it was used as a self-administered questionnaire (SAQ).

#### Management

Management of these patients was done according to the institute's protocol. Management consisted of medical therapy in the form of  $\alpha$ -blockers and 5AR Inhibitors. Surgical therapy was mainly Transurethral resection of prostate (TURP)

#### Post treatment evaluation

Evaluation following treatment was done at the end 3<sup>rd</sup> month. All patients were asked to come for follow-up at the end of 3<sup>rd</sup> month and were given the I-PSS & Male sexual function scale questionnaires. Uroflow with post void residue was also done to ascertain the effect of therapy.

#### **Correlation between LUTS & Sexual dysfunction;**

Correlation between LUTS severity and sexual function severity was assessed using Microsoft Excel correlation coefficient.

# **RESULTS & OBSERVATION**

All the patients who were admitted in our hospital for either evaluation (or) intervention of LUTS / BPH in the time period between July 2007 & December 2007 were enrolled for the study. After initial evaluation, 112 patients were excluded from the study as per exclusion criteria adopted.

Total enrolled	232
Co-morbid illness(DM /HT)	76
Already treated	16
No consent	20
Total Excluded	112
Included in study	120

The major cause for exclusion was associated co-morbid illnesses (Diabetes Mellitus or Hypertension (76 pts)). Finally 120 patients were included in the study.

# Age stratification

Age group	NO	%
50 - 59	23	19.1
60 - 69	73	60.8
70-79	23	19.1
> 80	1	0.8

The mean age of the patients is 64.5, in the range between 53 and 82. The majority (73) were in the age group of 60 - 69.

# LUTS severity stratification

LUTS severity and bother	No	%
Mild	16	13.33
Moderate	40	33.33
Severe	64	53.33
Total	120	100

Most of the patients (64, 53.33%) had severe bothersome symptoms

### Age group-wise LUTS severity

	Mild	Moderate	Severe	Total
50 - 59	9	9	5	23
60 - 69	4	27	42	73
70-79	3	4	16	23
> 80	0	0	1	1
Total	16	40	64	120

Most of the patients in the 50 to 59 age group (78%) had mild or moderately severe symptoms. In the 60-69 group 94.5% of patients had bothersome moderate to severe symptoms. Severe degree of symptoms were present in most of the patients in the 70 - 79 age group.

#### Prevalence of sexual dysfunction

# **Erectile dysfunction**

	No	%
None	29	24%
Moderate	60	50%
Severe	31	26%
Total	120	100

Most of the patients (50%) had moderate bother due to their erectile dysfunction. The rest had either no or severe bother in equal number.

Age Group	1	2	3	Grand Total
50-59	14	7	2	23
60-69	9	40	24	73
70-79	5	13	5	23
80-89	1			1
Grand Total	29	60	31	120

64 out of 73 patients in the age group of 60 moderate to severe erectile dysfunction, whereas, only 9 out of 14 patients had significant dysfunction in the age group of 50 - 59. The correlation coefficient for age and LUTS score is 0.33, signifying a positive correlation. As age increases the incidence of LUTS also increases.

# **Ejaculatory dysfunction**

	No	%
No / mild	80	67%
Moderate	39	32%
Severe	1	1%
Total	120	100%

Majority (66.6%) of the 120 patients had either no or mild bother due to their ejaculatory function. Only 1 was severely bothered.

Age Group	1	2	3	Grand Total
50-59	22	1		23
60-69	46	26	1	73
70-79	11	12		23
80-89	1			1
Grand Total	80	39	1	120

Just one patient in the age group of 50 -59 had significant ejaculatory dysfunction, whereas, 28 out of 96 patients above 60 yrs had significant ejaculatory dysfunction.

# Sexual desire disorder

	No	%
No / Mild	72	60%
Moderate	41	34%
Severe	7	6%
Total	120	100

Majority of patients (60%) were not at all bothered by their sexual desire disorder. 7 patients (6%) were severely bothered by their sexual desire disorder.

#### Sexual satisfaction

	No	%
Full sat.	50	41%
Mild dis	34	28%
Mod dis	29	25%
Total dis	7	6%
Total	120	100%

Among the 120 patients 50 (41 %) were fully satisfied with their sexual activities. Around 30% of patients were either moderately dissatisfied or totally dissatisfied.

Bother	No	%
None	36	29
Very Mild	7	6
Mild	29	24
Moderate	20	17
Severe	28	24
Total	120	100

Over all bother / distraction due to sexual dysfunction

Among the 120 patients 28 (23.3%) were very much bothered about sexual dysfunction. 20 patients (16.6%) were moderately bothered about their sexual dysfunction. Majority of patients (30%) not at all bothered about their sexual dysfunction.

Age Group	1	2	3	4	5	Grand Total
50-59	2	2	5		14	23
60-69	23	17	18	4	11	73
70-79	3	1	6	3	10	23
80-89					1	1
Grand Total	28	20	29	7	36	120

58 out of 73 patients in the age group 60 - 69 had bothersome sexual dysfunction. 25 out of 47 patients felt no bother due to sexual dysfunction in the other age groups.

#### Correlation between LUTS severity and sexual dysfunction bother

LUTS	No / Mild	Moderate	Severe	Total
Mild	16	0	0	16
Moderate	12	27	1	40
Severe	1	33	30	64
Total	29	60	31	120

### LUTS and Erectile dysfunction

All Patients with mild LUTS symptoms had none or mild erectile dysfunction, almost all of the patients in the severe LUTS group had moderate or severe erectile dysfunction.

The correlation coefficient is 0.71 showing significant positive correlation between LUTS and erectile dysfunction.

### **LUTS and Ejaculation**

LUTS	No / Mild	Moderate	Severe	Total
Mild	16	0	0	16
Moderate	35	5	0	40
Severe	29	34	1	64
Total	80	39	1	120

Only the patients with severe LUTS had ejaculatory dysfunction, 34 out of 40 patients.

The correlation coefficient is 0.5

	None	Very Mild	Mild	Moderate	Severe	Total
Mild	16	0	0	0	0	16
Moderate	13	5	14	7	1	40
Severe	7	2	15	13	27	64
Total	36	7	29	20	28	120

#### LUTS and sexual bother

None of the patients with mild LUTS symptoms were bothered by sexual dysfunction. Around 30% of patients with moderate LUTS had mild bother. 45% of patients with severe LUTS had severe distress due to sexual dysfunction.

The correlation coefficient is 0.65, significant positive correlation.

### **Treatment given**

Treatment	No	%
Medical	16	13%
Surgical	104	87%
Total	120	100%

After baseline evaluation among the 120 patients only 16 patients (13.3%) were eligible or willing to undergo medical therapy.

Patients (8) who had prostate volume of less than 30 cc were started on  $\alpha$  blockers. 8 patients had prostate volume of more than 30 cc and they were advised to take combination therapy ( $\alpha$  - blockers & 5-ARIs).

### **Medical Treatment**

α - blockers	8
5-ARIs	0
Both	8
Total	16

All patients had significantly improved flow rate and consequent reduction in I- PSS score.

#### Sexual function assessment

	Pre t	reatment	Ej.D	Post Treatment Ej.D					
	Mild	Mod	Sev	Mild	Mod	Sev			
α - blockers	8	0	0	6	2	0			
Both	8	0	0	4	4	0			
Total	16	0	0	10	6	0			

The erectile function was not altered after medical therapy. 6 patients (38%) developed bothersome ejaculatory dysfunction after medical therapy. 50% of patients on combined therapy and 25% on  $\alpha$  - blockers alone had ejaculatory dysfunction.

# Surgical therapy

Surgical therapy was mainly in the form of TURP. 104 patients underwent TURP under suitable anaesthesia. All patients had smooth postoperative period. All patients were asked to come for follow up at the end of 3 months. Only 34 pts turned up for repeat evaluation.

		ED		Ej.D					
	Mild Mod Sev				Mild Mod				
Pre Op	11	16	7	28	6	0			
Post Op	11	9	14	8	20	6			

Post operatively among the 16 patients who had moderate bother 7 patients (20%) had worsening of their erectile problems. Rest of the patients perceived no change.

Among the 28 patients who had no problems with ejaculatory function pre op, 20(71%) developed moderately bothersome ejaculatory dysfunction postoperatively. All the 6 patients who had moderate bother progressed to severe bother postoperatively.

#### DISCUSSION

Lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH), and sexual dysfunction, are common, highly bothersome conditions in older men, and the prevalence of both disorders increases with age. Sexual dysfunction manifests mainly as erectile dysfunction (ED), ejaculatory disorders (EiD), or decreased libido/hypoactive sexual desire (HSD). Men with moderate-to-severe LUTS are at increased risk for sexual dysfunction. The successful management of patients with LUTS associated with BPH should include assessments of sexual function and monitoring of medication-related sexual side effects. For men with LUTS and sexual dysfunction, an appropriate integrated management approach, based on each patient's symptoms and outcome objectives, is warranted. MSAM-7 study showed that there is progressive increase in LUTS and sexual dysfunction with age and independent increase in sexual dysfunction in patients with LUTS.

Out of a total of 232 patients who were enrolled into the study, 120 were finally included in the study after applying the inclusion and exclusion criteria. Though the sample size appears low, the patient group is the hospitalized patients only that form those who are very much distressed with the symptoms. Moreover the sample size is comparable with that of Namasivayam (et al)<sup>44</sup>. Patients with co-morbidities were

excluded from the study. They formed around one third of the patients. It is important to note that 10% of patients refused to respond to sexual health questionnaire, which carries significance.

The mean age of the patients was 65.8. The predominant age group is 60 - 69 yrs. This age characteristic is comparable to the studies in the literature. The elderly age may be significant, because age as such can have a bearing on sexual dysfunction as revealed in the Cologne Male Survey.

More than half of the patients had severe LUTS. This may be due to the patient sample selected, i.e. the in patient group. The LUTS symptoms also had age wise variation, with 78% of those in the 50 - 59age group with mild symptoms, and most of them in the 70 - 79 group with severe symptoms. This signifies increase in prevalence with age.

The sexual function too showed variation among different age groups. Both the factors, the erectile dysfunction and ejaculatory dysfunction were more common in the age group of 60 - 69, compared to other age groups. Only the patients in the age group 60 - 69 were significantly bothered by sexual dysfunction. This may be due to the association of sexual dysfunction with increasing age. Moreover patients after the age of 70 years may not consider their sexual dysfunction bothersome, though they have a high prevalence.

None of the patients in the mild LUTS group had ED whereas 98% in the severe group and 70% in the moderate LUTS group had significant ED. The increasing age is associated with both increase in LUTS and ED. This correlates well with the reports of the MSAM –7. The correlation coefficient for LUTS with ED is 0.71, which is highly significant. It is similar to the world literature.

The ejaculatory function was not that frequently affected By LUTS compared with ED. 67% of patients had no effect on their ejaculatory function regardless of their LUTS status. Whereas, in those affected, more than 90 % belonged to the severe LUTS group. This shows that though severe LUTS may not always associated with ejaculatory dysfunction, the presence of ejaculatory dysfunction signifies a higher LUTS status. These results correlate well with the study by Rosen RC et al who propose a prevalence of 70 –80 % sexual dysfunction with LUTS. The correlation coefficient is 0.5, signifying effective positive correlation.

The degree to which the patients are bothered by their sexual dysfunction also varies well with LUTS. Almost all the patients (27/28) who had severe bother due to sexual dysfunction had associated severe LUTS. None of them had mild LUTS. 30% of the patients with LUTS had no bothersome sexual dysfunction. This includes patients in the higher age group strata who may have significant dysfunction, but may

not be bothered by it. Around 89% of patients with severe LUTS had bothersome sexual dysfunction.

This bears evidence to the fact that sexual dysfunction increases with increasing LUTS. The MSAM –7 showed that the incidence of bothersome sexual dysfunction associated with LUTS. The correlation coefficient is 0.65, which shows that as LUTS increases, so too sexual dysfunction hand in hand requiring simultaneous effective management.

In the Government institutional set up, with predominantly poor patients, the standard medical management could not be given to the majority of the patients as they cannot afford it. So around 90% of the patients were taken up for TURP. Another problem with our patients is the poor compliance and lack of follow up. This is proved by the fact that only 34 out of 104 patients came for follow up after TURP.

In the post treatment evaluation after medical therapy, the ejaculatory function decreased in around 36% of the patients. This can be expected because retrograde ejaculation is one of the commonest adverse effect as associated with alpha blockers.<sup>27</sup> There was no change in the erectile function after medical therapy.

Out of the 34 patients who came for follow up after TURP, 20% of patients in the moderate ED progressed to severe ED. This may be due to the thermal injury to cavernosal nerves caused by TURP. 70% of the

patients developed ejaculatory dysfunction post operatively. This is also well explained in the literature.

To conclude, sexual dysfunction is highly prevalent in the patients with LUTS in the range of 70%. The age group should also be taken into consideration, because increasing age as such can lead to sexual dysfunction. As we do not have a control group we were unable to signify the influence of age. The severity of LUTS also correlated with severity of sexual dysfunction. The treatment outcome is not promising as the patients' ejaculatory dysfunction increased with both surgery and medical management. Though the sample size is small and the follow up is limited, we can suggest that treatment of sexual function should be combined with management of sexual dysfunction for better patient satisfaction.

# CONCLUSION

The prevalence of sexual dysfunction in patients with LUTS is 70%.

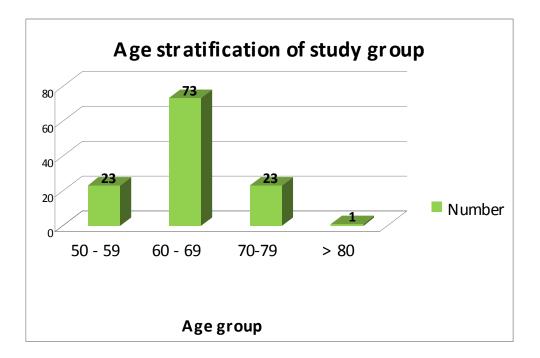
The severity of sexual dysfunction correlates with severity of LUTS.

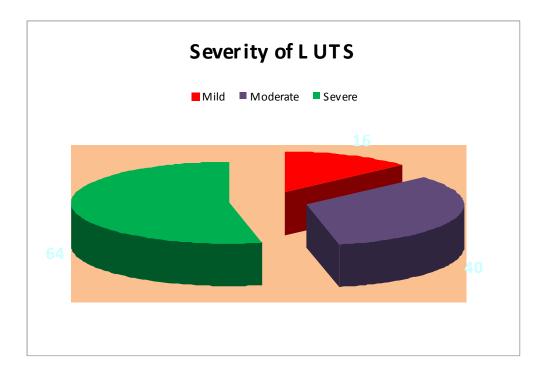
Ejaculatory function deteriorates after treatment of LUTS/BPH.

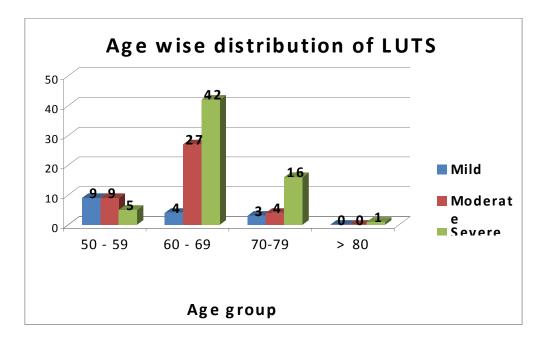
### **SUGGESTIONS**

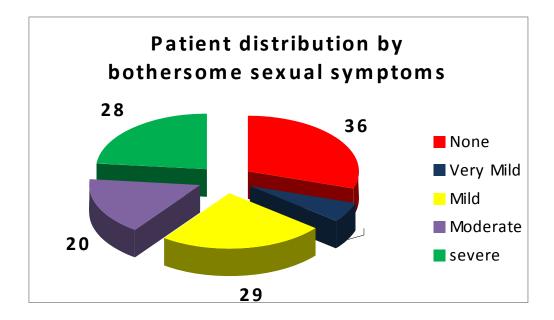
All patients with LUTS should be evaluated for sexual dysfunction

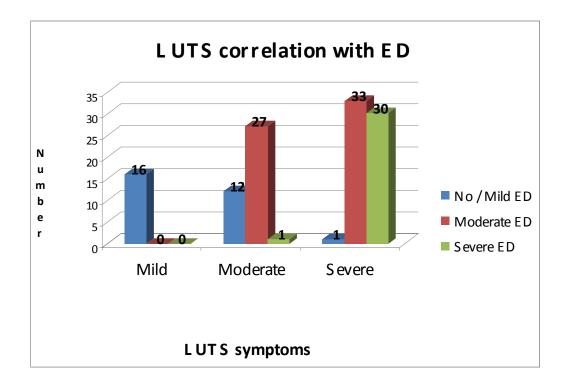
Treatment of sexual dysfunction should be combined with LUTS management for better patient satisfaction and quality of life.

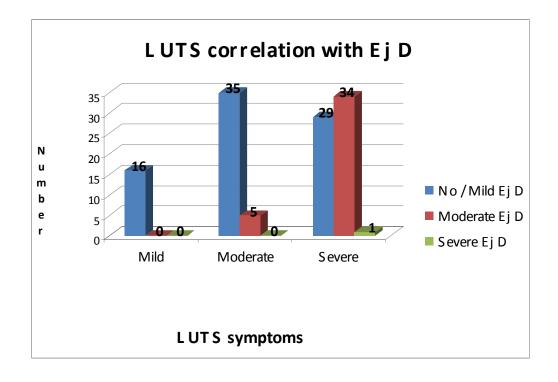


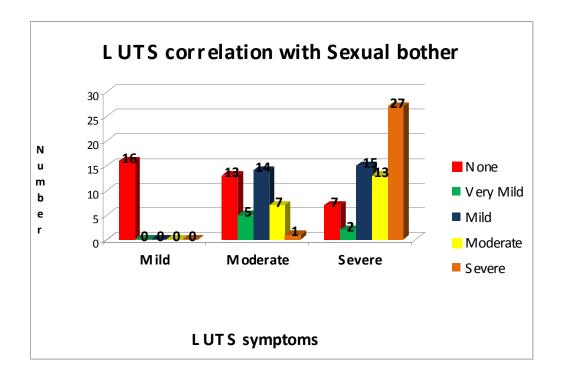












# PROFORMA

Name

Age

IP no:

Address

Duration of LUTS

Associated co-morbid illness

Clinical details

Investigations

**IPSS Score** 

MSF Scale

Treatment given

Post treatment IPSS & MSF scale

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C N.		LITO	DDE		ED	E.D	D		Dether	The second	Post tr	eatment
S.No.	Age	LUTS	DRE	LUTS score	ED	EjD	Desire	Satisfaction	Bother	Treatment	ED	Ej D
1	75	6 mo	Gr I	Severe	2	2	2	2	1	TURP		
2	60	4 mo	Gr II	Severe	2	2	1	3	1	TURP	2	2
3	70	6 mo	Gr I	mild	1	1	1	1	5	TURP		
4	60	8 mo	Gr II	Mod	2	1	1	1	3	TURP	2	1
5	75	6 mo	Gr II	Severe	2	1	2	4	1	TURP		
6	78	8 mo	GR I	mild	1	1	1	1	5	TURP	1	1
7	55	5 mo	GR II	Severe	3	1	1	1	1	TURP	3	1
8	65	6 mo	GR II	Severe	2	2	2	2	2	TURP	3	2
9	53	7 mo	GR II	Severe	3	1	1	1	2	TURP	3	1
10	60	6 mo	GR I	Mod	2	1	1	1	3	TURP		
11	80	5mo	GR III	Severe	1	1	1	1	5	TURP	1	1
12	57	4 mo	GR I	Mod	2	1	1	1	3	TURP		

# **MASTER CHART**

C N.		LITC	DDE		ED	E.D	During		Detler	T	Post tr	eatment
S.No.	Age	LUTS	DRE	LUTS score	ED	EjD	Desire	Satisfaction	Bother	Treatment	ED	Ej D
13	75	1 yr	GR II	Severe	2	1	2	3	3	TURP	3	1
14	61	8 mo	GR I	Mod	1	1	1	1	5	TURP	1	1
15	64	11 mo	GR I	Severe	2	1	1	1	3	TURP		
16	60	5 mo	GR II	Mod	2	2	1	2	2	TURP		
17	58	9 mo	GR I	mild	1	1	1	1	5	Medical	1	2
18	55	7 mo	GR I	Severe	2	1	1	1	3	TURP		
19	75	1 yr	GR II	Severe	2	2	2	2	5	TURP		
20	60	7 mo	GR I	Mod	2	1	1	2	3	Medical	2	1
21	55	6 mo	GR I	Mod	1	1	1	1	5	TURP		
22	75	18 mo	GR II	Severe	2	2	2	2	3	TURP	2	3
23	58	8 mo	GR I	Severe	2	2	1	3	2	TURP		
24	53	9 mo	GR I	Mod	1	1	1	1	5	TURP	1	1
25	77	1 yr	GR II	mild	1	1	1	1	5	TURP		
26	60	5 mo	GR I	Mod	2	1	2	2	2	TURP	2	2

			DDE	LUTC	ED	E.D	<b>D</b> ·				Post tr	eatment
S.No.	Age	LUTS	DRE	LUTS score	ED	EjD	Desire	Satisfaction	Bother	Treatment	ED	Ej D
27	72	8 mo	GR III	Severe	2	2	2	3	3	TURP		
28	57	6 mo	GR I	mild	1	1	1	1	5	Medical	1	1
29	78	18 mo	GR III	Severe	2	1	2	3	4	TURP	2	2
30	65	10 mo	GR II	Severe	2	1	1	1	3	TURP	2	2
31	65	4 mo	GR I	mild	1	1	1	1	5	Medical	1	2
32	60	6 mo	GR I	mild	1	1	1	1	5	Medical	1	2
33	74	11 mo	GR II	Severe	1	1	1	1	5	TURP	1	2
34	69	1 yr	GR I	Severe	2	2	2	1	3	TURP		
35	60	6 mo	GR I	Mod	2	1	1	2	3	Medical	2	2
36	65	9 mo	GR II	Severe	2	2	2	4	1	TURP	2	3
37	65	10 mo	GR II	Severe	2	1	1	2	2	TURP		
38	78	1 yr	GR II	Mod	2	1	1	1	5	TURP		
39	64	8 m0	GR I	Severe	3	2	2	3	1	TURP	3	3
40	70	18 mo	GR II	Mod	2	1	2	2	3	TURP		

C.N.		LITC	DDE		ED	E.D	Derte		Detles	T	Post tr	eatment
S.No.	Age	LUTS	DRE	LUTS score	ED	EjD	Desire	Satisfaction	Bother	Treatment	ED	Ej D
41	63	5 mo	GR I	Mod	2	1	1	2	2	TURP	3	2
42	66	7 m0	GR II	Severe	2	1	2	2	1	TURP		
43	60	6 mo	GR I	Severe	2	1	3	3	1	TURP		
44	71	1 yr	GR II	Mod	2	1	1	1	5	TURP	2	2
45	59	3 mo	GR I	mild	1	1	1	1	5	Medical	1	2
46	68	18 mo	GR II	Mod	2	1	1	3	3	TURP		
47	63	6 mo	GR I	Mod	2	2	2	2	2	TURP		
48	70	10 mo	GR III	Severe	2	2	1	2	4	TURP		
49	58	4 mo	GR I	mild	1	1	1	1	5	Medical	1	1
50	66	5 mo	GR II	Severe	3	2	3	3	2	TURP	3	3
51	57	6 mo	GR I	Mod	2	1	1	2	3	Medical	2	2
52	68	8 mo	GR II	Severe	2	1	2	2	2	TURP		
53	67	18 mo	GR II	Severe	3	2	2	2	2	TURP		
54	78	9 mo	GR II	Mod	1	1	1	1	5	TURP	1	2

C.N.		LITC	DDE		ED	E.D	During		Dether	T	Post tr	eatment
S.No.	Age	LUTS	DRE	LUTS score	ED	EjD	Desire	Satisfaction	Bother	Treatment	ED	Ej D
55	69	8 mo	GR III	Severe	3	2	2	3	3	TURP		
56	65	6 mo	GR I	Mod	1	1	1	1	5	TURP	1	2
57	58	4 mo	GR I	mild	1	1	1	1	5	TURP	1	2
58	68	9 mo	GR II	Severe	2	2	2	3	1	TURP	2	2
59	64	11 mo	GR II	Severe	2	1	2	3	1	TURP	3	2
60	63	8 mo	GR II	Severe	2	1	1	2	3	TURP		
61	60	6 mo	GR I	Mod	2	1	2	2	2	TURP		
62	58	5 mo	GR I	mild	1	1	1	1	5	Medical	1	1
63	70	18 mo	GRII	Severe	3	2	2	2	1	TURP		
64	68	4 mo	GR II	Severe	3	2	1	2	2	TURP		
65	59	6 mo	GR I	Mod	1	1	1	1	5	TURP		
66	67	10 mo	GR II	Mod	2	1	2	2	3	TURP		
67	65	9 mo	GR II	Severe	3	1	2	3	1	TURP		
68	65	7 mo	GR I	Mod	2	1	1	1	3	TURP		

C N.		TITO	DDE		ED	E:D	Destine		Dether	Treatment	Post tr	eatment
S.No.	Age	LUTS	DRE	LUTS score	ED	EjD	Desire	Satisfaction	Bother	Ireatment	ED	Ej D
69	59	6 mo	GR I	mild	1	1	1	1	5	TURP		
70	62	8 mo	GR II	Severe	3	2	3	3	1	TURP		
71	65	1 yr	GR II	Severe	3	1	3	3	1	TURP		
72	60	3 mo	GR I	Mod	2	1	1	1	5	Medical	2	1
73	60	8 mo	GR II	Severe	3	2	2	3	1	TURP		
74	76	10 mo	GRIII	Severe	2	2	2	2	4	TURP		
75	69	7 mo	GR II	Severe	2	1	1	1	3	TURP		
76	64	8 mo	GR I	Severe	3	2	2	2	2	TURP		
77	66	9 mo	GR II	Mod	2	1	1	2	3	TURP		
78	60	5 mo	GR I	mild	1	1	1	1	5	TURP	1	2
79	65	1 yr	GR II	Severe	3	2	2	3	1	TURP		
80	73	1 yr	GR II	Severe	3	2	2	3	2	TURP	3	3
81	69	10 mo	GR II	Severe	2	1	1	2	3	TURP		
82	70	6 mo	GR II	Severe	3	2	2	3	3	TURP	3	3

C N.		LITC	DDE		ED	E.D	During		Detler	T	Post tr	eatment
S.No.	Age	LUTS	DRE	LUTS score	ED	EjD	Desire	Satisfaction	Bother	Treatment	ED	Ej D
83	60	6 mo	GR I	mild	1	1	1	1	5	Medical	1	1
84	61	5 mo	GR I	Mod	2	1	1	2	2	TURP	3	2
85	64	8 mo	GR II	Mod	3	2	2	3	1	TURP		
86	58	6 mo	GR I	Mod	1	1	1	1	5	TURP	1	2
87	77	9 mo	GR II	Severe	2	2	2	3	5	TURP		
88	68	4 mo	GR II	Severe	3	2	2	4	1	TURP	3	2
89	64	8 mo	GR II	Severe	3	1	1	4	1	TURP		
90	65	6 mo	GR I	Mod	2	1	1	1	3	TURP		
91	60	5 mo	GR I	Mod	1	1	1	1	5	TURP	1	2
92	60	1 yr	GR II	Severe	2	1	1	1	4	TURP	3	2
93	62	10 mo	GR II	Severe	3	1	1	1	1	TURP		
94	67	8mo	GR II	Severe	2	2	2	3	1	TURP		
95	55	5 mo	GR I	mild	1	1	1	1	5	Medical	1	1
96	60	9 mo	GR II	Mod	2	1	1	1	4	TURP		

C.N.		LITC	DDE		ED	E.D	Dutin		Detler	T	Post tr	eatment
S.No.	Age	LUTS	DRE	LUTS score	ED	EjD	Desire	Satisfaction	Bother	Treatment	ED	Ej D
97	70	1 yr	GR II	Severe	3	2	2	3	3	TURP		
98	58	6 mo	GR I	Severe	2	1	1	3	1	TURP		
99	60	6 mo	GR I	Mod	2	1	1	1	5	TURP		
100	65	8 mo	GR II	Severe	3	1	1	2	3	TURP		
101	63	18 mo	GR II	Severe	3	2	2	3	1	TURP		
102	55	7 mo	GR I	mild	1	1	1	1	5	Medical	1	1
103	59	5 mo	GR I	Mod	2	1	1	1	3	TURP		
104	64	9 mo	GR II	Mod	1	1	1	1	5	Medical	1	1
105	67	10 mo	GR II	Severe	2	2	2	3	2	TURP	3	2
106	65	6 mo	GR I	Mod	2	1	1	2	4	TURP		
107	59	7 mo	GR I	Mod	1	1	1	1	5	TURP		
108	73	6 mo	GR II	Severe	3	2	2	2	5	TURP		
109	64	8 mo	GR II	Severe	3	1	1	2	2	TURP		
110	66	10 mo	GR II	Severe	3	2	2	3	1	TURP		

			DDE	LUTC	ED	E.D	<b>D</b> :				Post tr	eatment
S.No.	Age	LUTS	DRE	LUTS score	ED	EjD	Desire	Satisfaction	Bother	Treatment	ED	Ej D
111	63	6 mo	GR II	Severe	3	2	3	4	1	TURP		
112	60	5 mo	GR I	Mod	1	1	1	1	5	Medical	1	1
113	60	6 mo	GR II	Mod	2	1	1	1	4	TURP		
114	65	8 mo	GR II	Mod	2	2	1	3	2	TURP		
115	67	1 yr	GR II	Severe	3	2	3	4	1	TURP		
116	59	6 mo	GR I	Mod	2	1	1	2	3	TURP		
117	60	9 mo	GR II	Severe	3	3	3	4	1	TURP		
118	68	5 mo	GR II	Severe	3	1	1	2	3	TURP		
119	65	6 mo	GR II	Severe	2	1	2	2	2	TURP		
120	67	8 mo	GR II	Severe	3	2	2	3	1	TURP		

### Code

- Erectile Dysfunction (ED)
- 1 None
- 2 Moderate Bother
- 3 Severe Bother

- EjD Ejaculatory Dysfunction
- 1 None
- 2 Moderate Bother
- 3 Severe Bother

- **Overall Bother**
- 1 Severe
- 2 Moderate
- 3 Small
- 4 Very Small
- 5 No Bother

# **IP55 - INTERNATIONAL PROSTATE SYMPTOM SCORE SHEET**

பீராஸ்டேட்\_ சிகிச்சை தொடங்கும் முன்பாக BPH அறிகுறிகள் உங்களுக்கு எந்த அளவிற்கு இருக்கிறது என அறிந்து கொள்ள இது உதவியாய இருக்கும்.

- கடந்த ஒரு மாத காலத்தில் நீங்கள் சிறுதீர் கழித்து முடித்த பின்பு இன்னும் சரியாக போகவில்லை என்ற உணர்வுக்கு எத்தனை முறை உள்ளானிர்கள் ?
  - கடந்த ஒரு மாத காலத்தில் நீங்கள் சிறுநீர் கழித்த பின்பு இரண்டு மனி நேரத்திற்கு முன்பாக மீண்டும் எத்தனை கடவை சிறுநீர் கழிக்க வேண்டி வந்தது ?
- 3. கடந்த ஒரு மாத காலத்தில் நீங்கள் சிறுநீர் கழிக்கும்போது நின்று நின்று பல முறை கழிக்கும்படி எவ்வளவு தடவை ஏற்பட்டது ?
- 4. கடந்த ஒரு மாத காலத்தில் சிறுநீர் கழிப்பதை ஒத்திப் போடுவதில் உங்களுக்கு சிரமம் இருந்ததா ?
- கடந்த ஒரு மாத காலத்தில் எத்தனை தடவை மந்தமாக சிறுநீர் கழிப்பதாக உணர்ந்தீர்கள் ?
- 6. கடந்த ஒரு மாத காலத்தில் சிறுநீர் கழிக்க எத்தனை தடவை முக்கி முயன்று கஷ்டப்பட வேண்டி இருந்தது ?
- 7. கடந்த ஒரு மாத காலத்தில் நீங்கள் இரவு படுக்கைக்குச் சென்று காலையில் எழுந்திருக்கும் வரையில் எத்தனை தடவை சிறுநீர் கழிக்க எழுந்திருக்க வேண்டி இருந்தது ?

கீழே கொடுக்கப்பட்டுள்ள ஒவ்வொன்றிலும் உங்கள் எண்ணிக்கையின் மீது வட்டமிடவும்.

ஒரு போதும் இல்லை 1	5സ് - ഉപതലർത്ര ത്രത്രമണ്ട	அரை தடவைக்கு குறைவாக	குட்டத்தட்ட அரை தடவை	அரை தடவைக்கும் அதிகமாக	கிட்டத்தட்ட எப்போதும்
0	0	0	0	4	6
0	0	0	0	0	6
0	0	0	0	0	0
0	0	0	0	0	0
0	0	0	0	0	0
0	0	0	0	0	0
0	0	0	0	0	0
ஒரு போதும் இல்லை	1 தடலை	2 தடனவ	3 ഉപതല	4 தடவை	5 මුඬිනළා මුල්මින සුදු කෙන
0	0	0	0	0	G

\*

Abbet

இங்கே உங்கள் எண்ணிக்கையை கூட்டவும் வாத்த அற்குறி என்னிக்கை = விணக்களின் வொத்தம் 1 முதல் 7 =

மேலும் விவரமறிய உங்கள் டாச்டரிடம் கலந்தாலோசிக்கவும்

		Contra A	
			in adult

# MALE SEXUAL FUNCTION SCALE

	9 0 0 0 0	எதிரே குறி பாதிக்கப்	ப்பிட்டு பட்டுள்	ள்ள தொந்தரவுகளா ளீா்கள் என்று (✔) (	ல் நீங்கல தறியிட்டு	ா எந்த அளவு நிகாட்டவும்
	கடந்த மூன்று மாத காலத்தில் நீங்கள் உடலுறவு கொண்ட போது உங்களுக்கு ஆண் குறியில் விரைப்புத்தன்மை ஏற்படுகிறதா?	பாதிக்கப் படவில்லை	es di serio di	ஒரளவு பாதிக்கப் பட்டுள்ளேன்	203 203 0-1-0 (5 1-0)	மிகவும் பாதிக்கப் பட்டுள்ளேன்
	<ul> <li>ஆம், முழு விரைப்புத்தன்மையுடன்</li> <li>ஆம், பாதி விரைப்புத்தன்மையுடன்</li> <li>ஆம், குறைவான விரைப்புத்தன்மையுடன்</li> <li>இல்லை.</li> </ul>	0	0	6	9	6
	இல்லை.     இல்லை.     உடலுறவின் போது விரைப்புதன்மை முழுவதுமாக உள்ளதா?	Start Start	10.1 25	and in the second second	1000	and the second second
2.	உடலுறவன போது வரைப்புதனமை முழுவதுமாக உள்ளதா தும், ஆம், ஆனால் எல்லா நேரமும் இல்லை ஆம், எப்பொழுதாவது இல்லை, முழுமையாக இல்லை	0	0	6	4	6
3.	<ul> <li>இல்லால், முழுலையால் இல்லால்</li> <li>உடலுறவின் போது விந்து வெளியாகிறதா?</li> <li>ஆம்</li> <li>ஆம், ஆனால் எல்லா நேரமும் இல்லை</li> <li>ஆம், எப்பொழுதாவது</li> <li>இல்லை</li> </ul>	0	0	8	4	6
4.	விந்து வெளியாவது தாமதமாகிறது? இல்லை,			1 constant super		
	<ul> <li>ஆம், ஆனால் எல்லா நேரமும் இல்லை</li> <li>ஆம், எல்லா நேரமும்</li> <li>விந்து வெளியாகவில்லை</li> </ul>	0	0	8	0	6

	விந்து சீக்கிரமாக வெளியாகிறதா?					
	🔲 இல்லை,		6	0	6	
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	🗆 விந்து வெளியாகவில்லை	Company Public T3 A	and colorising a	Mary Marson	and the second	
	உங்களுக்கு உடலுறவில் எந்த அளவு ஆர்வம் இருக்கிறது?	and a state and a stat	and male ou		a layman	
	🔲 ஆம் எப்பொழுது போலும்			0	a subscription	
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	🗖 ஆர்வமே இல்லை	Heritome of the		-	11	
	உங்கள் உடலுறவு வாழ்க்கை திருப்திகரமாக உள்ளதா?	State State	CONCENCION OF CONCENCION	MEL	-	
	🔲 ஆம், மிகவும் திருப்திகரமாக உள்ளது	Sugara a stagenty	1 adamety since ber	and the sea	anito La	1.2
	🔲 ஆம், திருப்திகரமாக உள்ளது			12	D III	
	🗋 இல்லை, திருப்திகரமாக இல்லை,	teasing agyru	station through, do	2	D	
	🔲 மிகவும் திருப்திகரமாக இல்லை,		Contagen Chine H	100	The second second	
3.	கடந்த மூன்று மாதங்களில் உடலுறவு சம்மந்தமான	general a	ന്നലങ്ങളുക്ക .അത്ര	1	IJ.	
	தொந்தரவுகளால்	- Canal	मध्यक्रिया शिव्यक्षीय	uit Quint	Annale	
	எந்த அளவு பாதிக்கப்பட்டுள்ளீர்கள்?		4	2	P	
	🗆 மிகவும்	Chan Chan Chan and Chan	nciacieta cin tente los . de	6	<b>p</b>	
	🛛 ஒரளவு		สาระการสมุรรมสีกับระ	1000	1	
	🗆 சிறிதளவு		Section 2	2		
	🔲 மிகவும் சிறிதளவு		Cittania sono inte	mathere	aligne Se	
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