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Lower urinary tract disease: what are we trying to treat and in whom?

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The diseases of the lower urinary tract are traditionally divided into abnormalities of storage and abnormalities of emptying. The targets for therapy were the organs most responsible for influencing storage and emptying. Modern understanding places the symptomatic status of the patient as the overriding criterion for treatment. It also accommodates a broader understanding of multiple and overlapping systems. Symptoms of voiding dysfunction have been clearly shown to be associated with symptoms of other genitourinary disease, for example, erectile dysfunction (ED). Treatment of voiding dysfunction has also been shown to have effects (adverse or beneficial) in these other domains. Thus, the symptoms of lower urinary tract disease (LUTD) that have to be considered now as targets relevant to these therapies include ED, ejaculatory dysfunction, sexual desire, sexual pain disorders and female sexual dysfunction. The anatomic, neural and endocrine systems that support these symptomatic functions and dysfunctions span the range from the urogenital smooth muscle to the hypothalamus, the bladder sensory output to the micturition centre and growth factors to androgens. Potentially important targets also include vascular and spinal structures, sex hormones and nitric oxide as well as the obvious genes, enzymes and receptors. The epidemiological studies prove the convergence of LUTD when viewed through the lens of the current patient-related outcomes and problem constructs. This convergence serves as a clear guidance to include wide ranging outcome instruments in all future studies with compounds being investigated for the treatment of LUTD. Out of these will come evidence of expected and unexpected collateral effects. The convergence should open the possibility to a different business model for developing therapeutic concepts. The blockbuster drug for a monolithic indication may be supplemented by agents with single or multiple pathway activity with smaller parallel targets. Using an approach based on patient reported outcomes to therapeutic targets not only widens the range of conditions, but also the patient types who can be considered as having LUTD.
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Abbreviations: BPH, benign prostatic hyperplasia; ED, erectile dysfunction; FSD, female sexual dysfunction; HRQOL, health-related quality of life; ICS, International Continence Society; LUTD, lower urinary tract diseases; LUTS, lower urinary tract symptoms; OAB, overactive bladder; PE, premature ejaculation; PRO, patient-related outcomes; SUI, stress urinary incontinence; UI, urgency incontinence

Introduction

Lower urinary tract diseases (LUTD) are traditionally focused on voiding and were divided into abnormalities of storage and abnormalities of emptying. The targets for therapeutic intervention were the organs most responsible for influencing storage and emptying and their corresponding pharmacology. Modern understanding demands a broader understanding of the multiple and overlapping systems and places the symptomatic status of the patient as the overriding criterion for treatment. These two considerations guide any assessment of the populations at risk and the problems that may need remediation. They also change the way LUTD can be viewed.

The traditional problem groupings for LUTD include: lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH), urgency incontinence (UI), stress urinary incontinence (SUI), acute and chronic prostatitis, impotence and premature ejaculation (PE). More recent descriptions include overactive bladder (OAB) that was first identified in the indexed literature in 1989 (Fall *et al*., 1989). 'The Standardisation Subcommittee of the International Continence Society (ICS) now recognizes OAB as a 'symptom syndrome suggestive of lower urinary tract dysfunction.' It is specifically defined as 'urgency, with or without urge incontinence, usually with frequency and nocturia.' The ICS definition was not formulated until January 2001 and was not formally approved until September 2001' (Wein & Rovner, 2002). Erectile dysfunction (ED) was a formulation of the National Institutes of Health in 1992 (NIH, 1993). Female sexual dysfunction (FSD) was first recognized in an indexed publication in 1975 (Spano & Lamont, 1976) but as FSD it is another newcomer (Goldstein, 2000). PE was the preserve of clinical psychology from its early indexing in the 1950s to the mid-1990s when the link with selective serotonin reuptake inhibitors widened the therapeutic audience.

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The nature of the link between LUTS and BPH was clarified in the literature in 1995 (Reynard *et al*., 1995), although the interest in medical therapy for BPH was evident 2 decades earlier (Caine *et al*., 1976). The modern era of multiagent therapy for BPH and a literature led by industry started in the 1990s with finasteride (Stoner, 1990). BPH progression was recognized (Isaacs & Coffey, 1989) long before it became a clear therapeutic target (Roehrborn, 2000). BPH and ED were linked, other than as age-related diseases, more recently than anyone would suspect (O'Leary, 2000) and the clear epidemiological evidence was published even more recently (Braun *et al*., 2003). Although, many clinicians had clear suspicions and some investigators had the foresight to begin the search for the evidence some years previously (Boyle *et al*., 2003).

The links between ED, then called impotence, and depression stretch back into antiquity, but the discovery that there may be a two-way link (Seidman & Roose, 2000) and that this may be exploited therapeutically is recent (Nurnberg *et al*., 2002). The firm causal link between ED and cardiovascular disease is surprisingly recent (Kawanishi *et al*., 2001), although the problems of vascular disease in impotence have long been recognized (Scheer, 1960; Virag *et al*., 1985). The link between lipid disorders and ED was under early investigation in the 1990s (Junemann *et al*., 1991). The diabetes and ED connection was well established by the middle of the 20th century (Rubin & Babbott, 1958) as was the link with bladder dysfunction (Spring & Hymes, 1953). The link between ischaemia and bladder dysfunction was established in the 1980s (Vanarsdalen *et al*., 1983) although it is regarded as a very topical issue connecting the many faces of LUTD (Berger *et al*., 2005). The spinal cord and higher brain centres have long been recognized as major common factors regulating LUTD. A late-comer to the grouping is anal incontinence (AI). It is related to some of the more established LUTD at least as an association and in some conditions it shares a common cause (and consequently a possible common therapeutic strategy).

The new issues joining the former anatomic silos of LUTD into an inter-related web of conditions appear to be epidemiological (now often sponsored by industry), pharmacological (often led by industry) and symptom based. The last mentioned is observed in the trend to measuring patient-related outcomes (PRO) as is now often required from a regulatory standpoint. This bringing together of LUTD is arguably more based on current pharmaco-economic realities than on scientific leads or advances in 'omics' technologies. It is based more on the realization of multiple end-effects, possibly at different doses, and the economy of bringing one drug forward for more than one indication (Bilello, 2005).

Methods

In the following sections, a conceptual framework is developed that relates the current understanding of the problems to the pathophysiology of the diseases, the patient experience and the therapeutic interventions. This is developed as a context within which different LUTD present differently over time. It provides a basis for an exploration of the current view of the overlap in LUTD and the treatments. The epidemiology of LUTD can then be reviewed based on current literature and points to who might be treated. The review of clinical outcome instruments points to the current PRO, which can then be seen as a blend of original problem constructs and the reality of the modern complex healthcare environment. This brings into focus what could be treated in the context of interdependent LUTD.

The landscape for LUTD

The question of who to treat and what to treat arises for LUTD particularly because the problems are largely functional and not life threatening. The measure of risk is based on progression of the problem and quality of life and only rarely on serious morbidity. Infective complications from progression of BPH arose in only four out of more than 3000 men in 4 years of a study of medical treatment for BPH (McConnell *et al*., 2003). There is no record of a death rate from the presence of ED, although sudden death has been a subject of fascination when associated with intercourse (Bornstein, 1951) and was widely, and inaccurately, discussed in the popular press in the context of phosphodiesterase inhibitors for ED.

The development of the science influences how we identify LUTD. The translation of new molecular biological understanding into voiding parameters has to go through the imprecise step of measurement in a range of human subjects. The determination of what is important can be influenced by many things unrelated to the original basic science. This is inherently the issue with integrative science and its translation.

The complexity in LUTD comes to some extent from the late discovery of the inter-relatedness of pelvic conditions. When male voiding problems triggered an automatic transurethral resection, a silo was erected and labelled BPH. LUTS separated from BPH when Abrams and co-workers (Reynard *et al*., 1995) made the case only 10 years ago. Since then new medical therapies directed at functional aspects of LUTS (α-adrenoceptor antagonists) and BPH itself (5 α-reductase inhibitors) have steered the clinical literature. New minimal invasive treatments have further influenced clinical management of BPH over the last 10 years. Now the discussion of LUTS centres on quality of life (Haltbakk *et al*., 2005), LUTS and other symptoms (Seim *et al*., 2005) and broader considerations (Rohrmann *et al*., 2005). Nobody actually complains of BPH *per se*, unlike LUTS, so the patient-based focus of therapy has to be directed, not at what they are experiencing now, but at what they might experience later.

Complexity, or convergence of LUTD, is also found in that a treatment for LUTS is now evaluated for its impact on erection, ejaculation, depression and the partners (Mitropoulos *et al*., 2002). A treatment for ejaculation may derive from understanding gained in managing depression (McMahon & Touma, 1999). A treatment for complex incontinence (Norton *et al*., 2002) may derive from compounds first tested for antidepressant properties (Wong *et al*., 1988). The current understanding of the science may create the bridge between the various LUTD (Truss *et al*., 2000) or it may be more pragmatic or opportunistic. Out of the web of interactions some of current clinically important examples are epidemiologically: BPH/LUTS, BPH/ED; therapeutically (positive): OAB/depression, PE/depression, ED/LUTS, ED/depression; therapeutically (negative): BPH/ejaculation, BPH/libido; common risk factors: ED/libido/LUTS. The purpose of this analysis is not to provide an historical record for LUTD but to exemplify the variety of dimensions of LUTD.

Epidemiology, the patient experience and the treatments are three interlinked issues (Figure 1). The exact definition of any one significantly impacts on how the other two issues will be counted or considered. If there is an issue of priority it must favour the patient experience because ultimately in a condition where improving quality of life is the goal then this is how it is expressed. Increasingly, it is a reflection of the patient experience, rather than biological measures, that determines regulatory acceptance. The treatments are developed to satisfy that patient experience and are justified, in commercial terms, by the epidemiological picture.

However, the epidemiological picture is strongly influenced by how the questions are asked and what is studied. These are PRO and express in a predetermined way the patient experiences. The PRO are framed to satisfy selected actions of the treatments as well as patient experience. The epidemiological picture is not therefore the pure description of an objective disease state but a surrogate based on the view through the lens of the exact PRO measures used. Who needs treatment and what is being treated is determined by a fluid blend of the opportunity and the product.

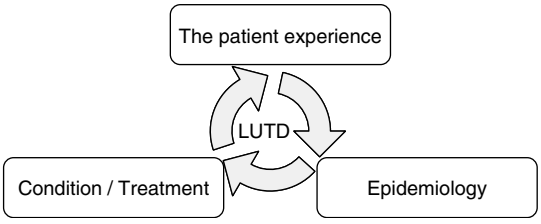

Figure 1 The cycle of patient experience, the epidemiology and the condition and the treatment for LUTD.

A more detailed look at the complex forces that go to shape the who and what of LUTD requires that this simple generalized interdependence is linked with the traditional elements of disease like anatomy, pharmacology and physiology. Figure 2 illustrates some of the inputs and their interactions to LUTD as experienced by patients. The multiple and overlapping systems derive from all the relevant organs in the pelvis and their major systemic support systems.

The anatomic substrates are represented as interlocking hexagons. Embryologically and functionally there are extensive overlaps. All of these are supported by vital systems that may both contribute to disease and/or share common origin. For example, diabetes mellitus has well-known effects on the cardiovascular system as a whole, the microcirculation of the bladder and its nerves, the smooth muscle of the bladder and the penis and impact on ejaculation and FSD. These local and systemic substrates are the biological entities that the science of LUTD is focused on. They are the subject of the other papers in this issue.

The functions and dysfunctions of these systems have been reduced to problem constructs in Figure 2 – a less definitive concept than diseases, syndromes or symptom complexes. Clinicians study, define and update these problem constructs. There is not a single term that has an absolute meaning – all require interpretation, understanding, consensus and perhaps definitions and guidelines. At the same time, these problem constructs are representations of patient complaints. Patients do not actually complain in the language of the problem constructs. Doctors do not always hear the true nature of the patient complaints. Patient complaints are strongly influenced by nonbiological environmental factors and partner, education and information are just three of a much larger number. It is because you can manipulate the environment that you can also

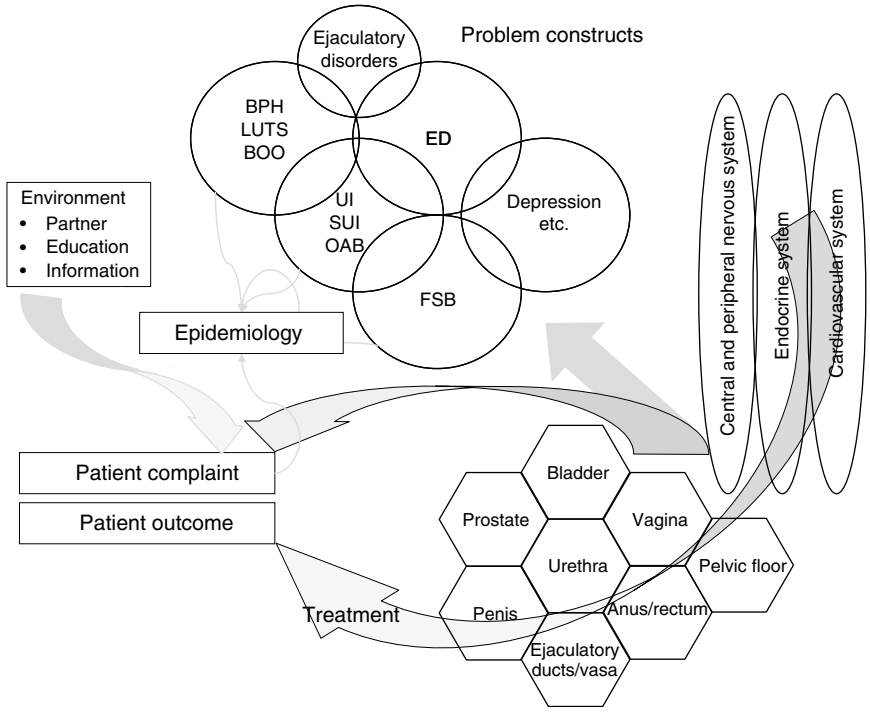

Figure 2 A conceptual map of the inter-relationships between the pathophysiology and anatomy of disease, the problem constructs and the consequent patient complaints and epidemiology (copyright reserved, J. Heaton).

manipulate the complaint (attentive management of a patient with LUTS may impact on their perception of symptom severity), hence one example of a need for placebo controls as well as a consideration of partner responses in properly constructed clinical trials.

Patient complaints and problem constructs define how the questions in epidemiological studies are framed. Armed with a definition of OAB it is possible to ask questions that require little interpretation that will reveal the presence, absence and degree of OAB. However, it is also possible to define incontinence in terms of dry days or best 3 out of 7 for pad use. The epidemiology of dry days is only that and any correlation of this with other measures of incontinence will have to be validated. ED is viewed through the prism of the International Index of Erectile Function (IIEF) (Rosen *et al*., 1997) but a man having no intercourse attempts in 3 out of the 4 weeks referred to in the questionnaire, because of jury duty perhaps, gives a false impression of his potency. So also the epidemiological picture gained from any study of LUTD will differ according to the patient complaints or problem constructs used.

The other factor in this landscape is the treatment. Based on the current understanding of the biology of the local and systemic factors contributing to LUTD treatments interact with the patient complaints to produce patient outcomes. And the circuit can move in reverse. An available biological effect can be used to create a patient outcome that is presented then as an important patient complaint and investigated epidemiologically, ultimately driving the creation of a problem construct or even a guideline. A positive variation on this theme is seen in the harnessing of adverse events as triggers for new therapeutic targets perhaps with dosing alteration (Pitsikas, 2000). A negative variation is the painting of a patient outcome as disease creation. An example might be the finding of improved libido in hypogonadal men with testosterone, which drives an epidemiological study that finds a high rate of hypogonadism and decreased libido that is then used to generate a market for testosterone for improving libido. This kind of exercise is denigrated as disease creation – fortunately the link between hypogonadism and libido has been known for millennia (Morley & Perry, 2003)! A more subtle and ambivalent tactic is to find a documentable effect, one that may have marginal clinical importance, and elevate it to treatable status by conducting epidemiological studies and publishing the results.

In this model, the biological systems are represented as having two consequences: the creation of patient complaints and the clinical version of those complaints, the problem constructs. The treatments are shown acting on those systems, modifying the patient complaints to cause patient outcomes. Thus, the outcome is viewed as a function of the complaint and the treatment and may contain elements of a number of conventional problem constructs. The treatments derive from increasingly precise understanding of the biology of the local and systemic structures and systems and are considered in other papers in this issue. No matter how selective the treatment for an LUTD appears, the actual patient outcomes will always reflect aspects of the complexity and convergence of these problems.

Following this framework, the choice of disease to be treated comes from insight into the current problem constructs and the creation of a business model for an available scientific strategy that will favourably impact a chosen disease. The business model will depend on an epidemiological understanding of the disease. If the candidate drug is one of a therapeutic class, the patients to be treated will be better understood and comparative data will be available. If the proposed treatment is novel in its mechanism of action, the proper questions to ask in an epidemiological study will only become apparent after the drug has been tested. The patient complaints and patient outcomes may not exactly comply with the conventional problem constructs. That explains the proliferation of PRO scales (vide infra). It also favours the increasingly popular strategy of securing new uses for existing molecules.

Selected epidemiological highlights

Clearly, the exact epidemiological information depends on the questions asked, as pointed out earlier (Vandoninck *et al*., 2004). A clear picture of who suffers from what is therefore fragmented into many viewpoints by the scales used.

The simple answer to the question of what and who to treat with BPH comes from the literature such as that reporting on BPH in Olmsted County (Bruskewitz, 1999). In men from 50 to 80 years of age, the number of men with significant IPSS scores ranged from 17%, through 27 to 37% by decade. Management is split between primary care physicians (25% of cases), internal medicine (24%) and urologists (37%). The goal of treatment was improvement in urinary symptoms and quality of life. In men with moderate symptoms medical therapy was used in 80–90% and TURP in 1–9%. Without an upheaval in therapeutic strategies, the vision of future management could be said to involve treating more men with more medications.

In the following capsule descriptions of current problem constructs, there is epidemiological information that helps define the patients. Presumably in each is also an LUTD cycle of patient issues such that the condition creating the patient experience generates the epidemiology and the treatment. If you shift the definition at any point, the other issues will follow. The example of OAB has already been mentioned – until this term was formulated there were no treatments for it. If the concept of specific treatment for urgency is introduced to the standard LUTS associated with BPH then measures will have to be made to modify the epidemiology of this 'new' subcategory to capture this patient experience and the 'new' treatment. The picture of the condition is only accurate for its current definition.

Overactive bladder

Incontinence is found with a rate of 7.3%. Incontinence (no obvious cause) was found to be troublesome in 73%, nocturnal incontinence in 69% and nocturia in 63%. The symptoms are not always regarded as bothersome and do not always require treatment (Swithinbank *et al*., 1999).

Lower urinary tract symptoms

Severe LUTS was seen in 19.2% of men and 13.7% of women and UI in 73% of men and 29% of women in a telephone survey. Among men and women reporting only one-third with

severe symptoms of UI had been treated (Fourcade *et al*., 2002).

Benign prostatic hyperplasia

The Olmsted County study (1987–1997) identified an age-adjusted, corrected incidence for BPH of 854.7 per 100,000 men. Over the 10 years age-adjusted incidence decreased, surgical treatments decreased and rates of pharmacological treatments increased (Sarma *et al*., 2005).

BPH and LUTS

The incidence of OAB increases in the absence of increasing outlet obstruction, hence it is not possible to state definitively that LUTS is caused by BPH (in men) although it is clearly associated (Thomas & Abrams, 2000).

BPH associated with LUTS and ED

All increase in prevalence with age (from many studies) (Feldman *et al*., 1994; Milsom *et al*., 2001). Review papers point clearly to the collision of BPH, LUTS and sexual symptoms (Rosen *et al*., 2005) without the equivalent pathophysiological clarity or causality (McVary, 2005).

In four centres, the prevalence of ED increased with age and the odds ratio (OR) of 1.39 for LUTS (as measured by IPSS) was similar to diabetes (1.57) and hypertension (1.38) (Boyle *et al*., 2003).

LUTS was found associated with deterioration in sexual life in 8% of community men and 46% in the clinic. Older men were less bothered. The ORs for ED with voiding parameters ranged from 1.61 to a high of 5.63 for nocturnal incontinence. Storage symptoms (associated with incontinence) but not urinary flow rates were found associated with sexual symptoms (Frankel *et al*., 1998).

Both ED and ejaculatory dysfunction increased with age and IPSS in another study (Vallancien *et al*., 2003).

Risk factors

Current cigarette smokers had no higher odds of LUTS than 'never' smokers, but former heavy smokers, but not current smokers, had a higher ratio (2.01) for LUTS. Sedentary men had a higher ratio (2.06) and drinking was protective (OR of 0.59) as was moderate and vigorous activity (Rohrmann *et al*., 2005).

The risk profile is similar for ED with diabetes, heart disease, hypertension, cerebrovascular disease and smoking (4.6%) associated with an increased risk of ED (Shiri *et al*., 2004).

Incontinence and depression

Among women with incontinence, major depression prevalence rates increased with incontinence severity and type. Major depression in women with urinary incontinence was increased by obesity (OR 2.3) and current smoking (OR 2.7) (Melville *et al*., 2005).

In men, the total burden of LUTS is related to self-assessed sadness (Engstrom *et al*., 2005).

Current clinical outcomes in LUTD

The importance of PRO in defining epidemiology, therapeutic targets, problem constructs and gaining regulatory approval has increased to a high level currently. The profusion of scores and scales indicates the extent of the inter-relatedness of LUTD and also the importance of an exact, custom or sometimes a friendly outcome variable.

In launching the new NIH PRO initiative Director Elias A. Zerhouni, MD said 'There is a pressing need to better quantify clinically important symptoms and outcomes that are now difficult to measure. Our clinical research communities would benefit greatly from efficient, consistent, well-validated approaches to measuring these and other subjective outcomes.' The introduction goes on to point out that 'Clinical measures of outcome such as x rays and lab tests have minimal relevance to the day-to-day functioning of patients with such chronic diseases as arthritis, multiple sclerosis, and asthma, as well as chronic pain conditions. Often, the best way patients can judge the effectiveness of treatments is by changes in symptoms. One goal of the PROMIS initiative is to develop a set of publicly available computerized adaptive tests for the clinical research community' (NIH, 2005).

A similar exhortation has been published by one of the experts 'Obviously, it is important to use (or devise) a universal questionnaire that evaluates from the patient's standpoint the amount and frequency of incontinence, bothersomeness (including inability or reluctance to engage in certain activities) and overall quality of life' (Wein & Rovner, 2002). While the intent was to draw attention to the difficulty of acquiring data in one small aspect of LUTD (the surgical results for incontinence) the concept is relevant for all LUTD.

The danger of universally accepted PRO instruments is that a generation of drugs is evaluated against a scale that may be biased or limited in its scope. The benefit is clearly that drugs will be judged against a single standard. An additional problem is that a lack of diversity in measures limits the likelihood of benefiting from unexpected outcomes.

The following list of evaluative tools demonstrates the drive to produce a scale suitable to the study at hand, the importance of PRO, the crossover between various LUTD and the need to understand the provenance and limitations of the scores used.

Caution – authors may use their own variations on the acronyms for a scale, this contributes to confusion and may explain omissions and duplications in this list.

AUA-SI (American Urological Association Symptom Index) (Barry *et al*., 1992) includes seven questions covering frequency, nocturia, weak urinary stream, hesitancy, intermittence, incomplete emptying and urgency.

BFLUTS (Bristol Female Lower Urinary Tract Symptoms) (Brookes *et al*., 2004) three domains assess symptoms: incontinence (three items); voiding (three items); and filling (four items); with additional subscales for sexual function (two items) and quality of life (five items).

BII (BPH Impact Index) (Barry *et al*., 1995) measures how much urinary problems affect various domains of health. See also BPHII (Namasivayam *et al*., 1998). An example of its use: sexual function scores were better correlated with BPHII scores than with the total IPSS, although some of the individual IPSS questions correlated well.

BISF-W (Brief Index of Sexual Functioning for Women) (Taylor *et al*., 1994) is a 22-item, self-report instrument for the assessment of current levels of female sexual functioning and satisfaction.

BSFI (Brief Sexual Function Inventory also seen as SFI) (O'Leary *et al*., 1995) covers: sexual drive (two items), erection (three items), ejaculation (two items), perceptions of problems in each area (three items) and overall satisfaction (one item).

BSW (Benefit, Satisfaction and Willingness) scale: perception of treatment benefit, satisfaction with treatment, and willingness to continue treatment as used for treatment evaluation.

CMSH-SFQ (Center for Marital and Sexual Health Questionnaire) (Corty *et al*., 1996) for male patients and their partners. The CMSH-SFQ measures erectile and orgasmic functioning, sexual drive, frequency of sexual behaviour and sexual satisfaction.

CONTILIFE (Jeffry *et al*., 2001), a questionnaire aid to the assessment of subjective cure rate for the tension-free vaginal tape (TVT) procedure in women with urinary incontinence.

CSFQ (Changes in Sexual Functioning Questionnaire) (Clayton *et al*., 1997), a structured interview/questionnaire designed to measure illness- and medication-related changes in sexual functioning. See also CSFQ-F-C (Warnock *et al*., 2005) and a parallel scale, the CSFQ-M-C.

Dan-PSS Sex (Danish Prostate Symptom Score Sexual Function Questionnaire also SEX DanPSS) (Tuhkanen *et al*., 2001) includes items concerned with erectile stiffness, ejaculatory volume and pain or discomfort on ejaculation.

DAN-PSS-1 (Danish Prostate Symptom Score), a scoring system based on the severity of 12 symptoms related to bladder storage and voiding function, and three questions related to sexual function. The DAN-PSS index is more sensitive than the IPSS, Madsen-Iversen and Boyarsky symptom indices, incorporates important outcome events, and includes a patient-weighting of each symptom, thereby reflecting better the patients' global assessment of outcome (Hansen *et al*., 1998).

DISFSR FEMALE and DIFSR MALE (Derogatis Interview for Sexual Functioning) (Derogatis, 1997), a set of brief, gender-keyed, multidimensional outcome measures designed to measure quality of sexual functioning.

ED-EQOL (Erectile Dysfunction Effect on Quality of Life, also known as QOLQED) (MacDonagh *et al*., 2002) is an instrument for quantifying the effect of ED on quality of life.

EDITS (Erectile Dysfunction Inventory of Treatment Satisfaction) (Althof *et al*., 1999) is a scale for assessing treatments for ED. Out of 29 items representing the domains of treatment satisfaction for men and 20 representing partner satisfaction 11 patient items met criteria and form the Patient EDITS; five partner items met criteria and form the Partner EDITS.

EPIQ (Epidemiology of Prolapse and Incontinence Questionnaire) (Lukacz *et al*., 2005), a screen for female pelvic floor disorders including: pelvic organ prolapse (POP), SUI, OAB and AI.

FSDS (Female Sexual Distress Scale) (Derogatis *et al*., 2002) measures sexually related personal distress in women. The original 20-item version was reduced to a 12-item final version that distinguishes sexually dysfunctional and functional women and a strong sensitivity to treatment response.

FSEP (or FSEPA) (Female Sexual Encounter Profile) (Padma-Nathan *et al*., 2003), an arousal success rate measured by diary responses.

FSFI (Female Sexual Function Index) (Rosen *et al*., 2000) has six domains (desire, subjective arousal, lubrication, orgasm, satisfaction, and pain). The scale pointed to important gender differences in the patterning of female sexual function in comparison with similar questionnaire studies in males (BSFI).

F-SFQ (Female Sexual Function Questionnaire) (Quirk *et al*., 2002), seven domains of female sexual function for evaluating treatments of these disorders: desire, physical arousal-sensation, physical arousal-lubrication, enjoyment, orgasm, pain and partner relationship.

GRISS (Golombok Rust Inventory of Sexual Satisfaction) (Rust & Golombok, 1985), a 28-item questionnaire for assessing the existence and severity of sexual problems.

ICIQ (International Consultation on Incontinence Questionnaire also available as a Short Form) (Avery *et al*., 2004) applicable as an outcome measure in patients with stress incontinence, it includes a measure of quality of life impact in a short format.

ICSmale (International Continence Society-male) (Donovan *et al*., 1996) comprises questions concerned with urinary symptoms, the bother they cause and issues of quality of life and sexual function. Developed for the International Continence Society – 'Benign Prostatic Hyperplasia' study, there was reasonable agreement between relevant parts of the questionnaire and frequency–volume charts, but there was a poor relationship between questions assessing strength of stream and the results of uroflowmetry.

IIEF (International Index of Erectile Function) (Rosen *et al*., 1997), the final 15-item questionnaire has been widely validated and has five domains (erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction). It has become the definitive standard for evaluation of erectile function.

IPSS (International Prostate Symptom Score, I-PSS) (Barry *et al*., 1992) was proposed during the First Consultation on Benign Prostatic Hyperplasia in June 1991. Based on the AUA symptom score, it includes a patient weighting of the symptoms in terms of the impact on the quality of life of the patient.

I-QOL (Incontinence Quality Of Life) (Wagner *et al*., 1996) is a self-report quality of life measure specific to urinary incontinence that can be used as an outcome measure in clinical trials and in patient care centres.

KHQ (King's Health Questionnaire) (Kelleher *et al*., 1997), a valid and reliable instrument for the assessment of quality of life in women with urinary incontinence useful for the rapid appraisal and follow up of women with urinary incontinence.

MFSQ (McCoy Female Sexuality Questionnaire) (McCoy & Matyas, 1996) Original version: 19 items, also validated in a short form.

MHQ (Manchester Health Questionnaire) (Bug *et al*., 2001) is both a valid and reliable instrument for the assessment of health-related quality of life among women with AI.

MOS-SEXUAL (Medical Outcomes Study: Sexual Problems) is a component of the Rand Health quality of life instruments.

MSF-4 (Male Sexual Function 4-item) (Marquis & Marrel, 2001) questionnaire is a condition-specific four-item scale of men's sexuality that allows easy and appropriate assessment of male sexual function in the clinical setting.

MSIQ (Menopausal Sexual Interest Questionnaire) (Rosen *et al*., 2004), a 10-item scale with domains of sexual function with a focus on sexual interest and desire.

NIH-CPSI (Litwin *et al*., 1999), an index of nine items that addresses three different aspects of the chronic prostatitis experience: pain, captured in four items focused on location, severity and frequency, urinary function, captured in two items (one irritative and one obstructive), quality of life impact captured in three items about the effect of symptoms on daily activities.

OABQ (Overactive Bladder questionnaire or OAB-q and also a short form) (Coyne *et al*., 2002; 2005) is a 33-item self-administered questionnaire that contains a symptom bother and HRQL scale and is responsive to reductions in urinary urgency, frequency and incontinence during antimuscarinic treatment of OAB.

PAIRS (Psychological and Interpersonal Relationship Scales) (Swindle *et al*., 2004) is to evaluate the broader psychological and interpersonal outcomes associated with ED: the domains captured include sexual self-confidence, spontaneity and time concerns.

PAIRS-SF (Psychological and Interpersonal Relationship Scales Short Form) (Swindle *et al*., 2005) is a brief measure of psychological and interpersonal outcomes associated with ED and measures sexual self-confidence, spontaneity, and time concerns.

PDQ (Psychosexual Daily Questionnaire) (Lee *et al*., 2003) records and scores parameters for sexual desire, sexual enjoyment, sexual performance, sexual activity, and positive and negative moods daily for 7 days before a clinic visit.

PEQ (Personal Experiences Questionnaire) (Dennerstein *et al*., 1997) used to assess the relationship of sexual functioning to age, menopausal status and hormone levels, six factors are measured: (1) feelings for partner, (2) sexual responsivity, (3) sexual frequency, (4) libido, (5) partner problems and (6) vaginal dryness/dyspareunia.

PFSF (Profile of Female Sexual Function also seen as FSDP Female Sexual Desire Profile) (Derogatis *et al*., 2004) is a patient-based instrument for the measuring of loss of sexual function in menopausal women with low libido (hypoactive female sexual desire disorder). It has 37 items in seven domains (sexual desire, arousal, orgasm, sexual pleasure, sexual concerns, sexual responsiveness, and sexual self-image) and a single-item measure of overall satisfaction with sexuality.

PGIIS (Patient Global Impression of Improvement Scale) (Patrick *et al*., 1999) for mixed incontinence correlates significantly with incontinence episode frequency, stress pad test, and Incontinence Quality of Life Questionnaire measures.

POSQ (Primary OAB Symptom Questionnaire) (Matza *et al*., 2005).

PPBC (Patient Perception of Bladder Condition) (Matza *et al*., 2005).

QOL9 (Quality-Of-Life Questionnaire) (Lukacs *et al*., 1997) BPH-specific, it includes an assessment of patients' perceived sexual-life status.

QUALIVEEN (Costa *et al*., 2001) a urinary disorder-specific health-related quality of life (HRQL) instrument questionnaire originally developed in French and trade marked.

SAIL (Scale for Activity Interference and Limitation 1, 2 and M) used in phase III trials of treatment for mixed incontinence.

SAL (Sexual Activity Log) used in phase III trials of testosterone for FSD.

SAQ (Sexual Activity Questionnaire or SEXACQ) (Thirlaway *et al*., 1996) was developed to investigate the impact of long-term tamoxifen on the sexual functioning of women at high risk of developing breast cancer. It was tested on a sample of women with no such risk and measured pleasure from sexual intercourse (activity), pleasure and discomfort during sexual intercourse and habit.

SEAR (Self-Esteem And Relationship) (Cappelleri *et al*., 2004), 14 items in two domains: sexual relationship (eight items) and confidence (six items in a four-item self-esteem and two-item overall relationship subscale). For measuring sexual relationship, confidence and particularly self-esteem.

SEP (Sexual Encounter Profile) (Hellstrom *et al*., 2003), a patient measure of success rates for penetration (SEP question 2) and maintenance of erections (SEP question 3).

SES (Sexuality Experience Scales) (Anderson *et al*., 1992).

SHIM (Sexual Health Inventory for Men or IIEF-5) (Rosen *et al*., 1999) is a convenient way to rapidly identify patients at high risk for ED who should be further assessed. The moderate-to-high correlation and agreement between the SHIM and patient self-assessment of ED validate the SHIM for use in the diagnostic classification of ED severity.

SLOQ (Sexual Life Quality Questionnaire) (Woodward *et al*., 2002) consists of 16 items, 10 of which deal with sexual QOL and six items comprising a scale measuring satisfaction with treatment dimensions.

SPI (Symptom Problem Index) (Barry *et al*., 1995) captures how troublesome patients find their urinary symptoms and clarify how BPH affects overall health status and function.

TSS (Treatment Satisfaction Scale) (DiBenedetti *et al*., 2005), six scales are used as a multidimensional measure of satisfaction with ED treatment for patients and their partners: 'satisfaction with medication,' 'ease with erection,' 'satisfaction with erectile function,' 'pleasure from sexual activity,' 'satisfaction with orgasm,' and either 'sexual confidence' (for patients) or 'confidence in completion' (for partners).

U-IIQ (Urge-Incontinence Impact Questionnaire) (Lubeck *et al*., 1999), an HRQOL for patients with urge incontinence contains nine items summarized in a single score that measures the extent to which incontinence symptoms bother patients and an urge symptoms summary score.

UPS (Urgency Perception Scale) (Cardozo *et al*., 2005), an indicator of perceived urinary urgency in clinical studies evaluating the efficacy of antimuscarinic drugs. It is also a scale by which urinary urgency can be assessed subjectively for research into treatments for urinary urgency.

UQ (Urgency Questionnaire) (Matza *et al*., 2005).

Urogenital Distress Inventory-Short Form (no information).

UROLIFE (Urolife BPH QoL 20) (Lukacs *et al*., 1998) is a 20-item BPH-specific health related quality of life score, which includes three questions on sexuality.

USQ (Urinary Symptoms Questionnaire) (Abrams *et al*., 2003), a score on aspects of urinary symptoms associated with spinal cord injury and treatment.

UUDI (Urge-Urinary Distress Inventory) (Lubeck *et al*., 1999), an HRQOL for patients with urge incontinence contains 7 scales scored separately: travel, activities, physical activities, feelings, relationships, sexual function and nighttime bladder control.

Discussion

The convergence of LUTD emerges whether the problem is approached from the scientific standpoint, from an epidemiological standpoint or from the view of the patient. Previous studies (as well as ones contained in this issue) have established that there is scientific convergence based on links between structural and functional components. This integration also exists for afflicted patient, a suggestion that is supported by epidemiological evidence. This merging of understandings probably indicates that medicine is approaching the truth with a more flexible view than previously. It also, parenthetically, shows that it is important to analyse clinical problems such as LUTD with integrative physiology constructs. Specifically, we cannot reduce the whole to isolated subsystems without risking a serious misunderstanding of the larger picture.

The epidemiological studies prove the convergence of LUTD when viewed through the lens of the current PRO and problem constructs. Although a full causative explanation for convergence has not been attempted here, a number of studies have found ORs confirming the general concept – without any information regarding cause. There are obvious mechanistic explanations why some LUTD should be linked – such as urgency (represented by urgency and UI) and the obstructed bladder (described as BOO and related to decreased flow rates and acute and chronic urinary retention). The original concepts in this area were associated with issues of bladder instability associated with outlet obstruction (Ramsden *et al*., 1977) and animal data looking at the same phenomenon (Speakman *et al*., 1987) also stressed the concept of bladder instability. The clinical use of the term urgency places the emphasis on the patient experience rather than the bladder physiology (Blaivas, 1990) and becomes the dominant term in clinical usage. Thus, physiology, terminology and epidemiology allow that urgency and obstruction are associated and in this case there is a causative relationship. Other LUTD show similar associations with greater or lesser degrees of causative resolution. It is important to realize, however, that causative explanations may not always lie locally, but also in the spinal cord and central nervous system or in the supporting systems at a macro level (cardiovascular, endocrinologic, etc.) or microlevel (receptor, genomic, etc.).

The patient experience demonstrates convergence, not because human physiology has changed, but because the questions are now being asked more carefully and the answers recorded as data. For instance, few trials of drugs for LUTS would be acceptable today without careful documentation of sexual, and probably partner, secondary end points. This comes about partly as a result of the recognition of the overlap of beneficial and adverse effects in lower urinary tract treatments on various parameters of lower urinary tract function. Just as there are physiological links between LUTD, so there is great potential for spillover of effects, good and bad, from therapies of those LUTD.

The convergence serves as a clear guidance to include wide ranging outcome instruments in all future studies with compounds being investigated for the treatment of LUTD. The emphasis on the patient experience is understandable in this context. Fixed concepts of patient experience, approximating the problem constructs in the textbooks, are insufficiently flexible and sympathetic to actual patient experience. Diversity in measurement tools is good but, when left unchecked or validated, it leads to designer instruments and overlapping, but ultimately obstructive descriptions. The initiative for clarity in descriptive language in other areas of medicine (Stearns *et al*., 2001) could similarly be helpful in this clinical realm here if the political overtones of problem definition by academic societies and other parties could be resolved. Clearly, there is diversity in patient experience, there are overlaps in the patient complaints in the LUTD and there is significant flexibility in the description of PRO, such that there should be, at least in part, a common therapeutic strategy for similar conditions. Common language and careful definition may result in universal and even flexible PRO for LUTD. However, it is unlikely that this would displace the commercial incentive to express a condition and a PRO to suit a potential therapy.

A positive aspect of convergence in LUTD and the more widespread evaluation of multiple PRO for therapies will be the finding of expected and unexpected collateral effects – or PRO. By looking with less focused instruments at PRO, there will be the prospect of multiple benefits in a range of LUTD from individual therapies. In addition, the availability of multiple pathway effects with single chemical entities (e.g., noradrenergic and serotoninergic effects in a single molecule) emphasizes the value of broad coverage of PRO instruments.

The potential for a therapeutic strategy based on convergent LUTD is that diversity of response (selective vs non-selective actions) for single chemical entities or combinations of drugs could provide the basis for better treatment. Multiple effects have traditionally been a burden to the pharmaceutical companies who seek to create single clear indications and realize economies of scale (blockbuster drugs). A different business model could be applied to developing therapeutic concepts if they were recognized to have broader benefits in overlapping but not identical conditions. The blockbuster drug for a monolithic indication may be supplemented by agents with single or multiple pathway activities with smaller parallel targets, or in its broadest application the development of the 'polypill'.

The future development of targets based on this understanding remains largely hidden. The manoeuvring to achieve an exact PRO that proves the benefit and supports the epidemiological picture comes at a point in a drug development process where the outcomes are closely predicted. The candidate therapies themselves and the new concepts are largely out of sight, hidden by the density of competing concepts. Usually, the new PRO instruments emerge as the drugs surface and the epidemiological studies follow. All of this adds diversity to the field of LUTD and enables significant investment that eventually benefits patients and prescribers. It does not necessarily provide clarity or evidence of clinical priority within the LUTD.

In exploring the issue of what and who to treat regarding LUTD, the material reviewed has covered what would be required to practice or establish treatments based on evidence. The evidence is based on epidemiology, PRO, terminology and clinical trials. The development of evidence-based medicine (EBM) has taken place over the same period of time as is covered by the development of LUTD as a common therapeutic target (EBM, 1992). The strength in the EBM paradigm has been in proving the clinical value of the therapies

that are available. A problem is that EBM only proves what is possible with what is available and it does not itself open up new possibilities. It is also dependent on the PRO and problem constructs in use at the time. Convergence of the LUTD, necessitates the application of a broad catchment for new PRO and an open mind.

The simple answer to the question of what and who to treat with BPH may come from the literature such as that reporting on BPH in Olmsted County (Bruskewitz, 1999). It should take into account a broader range of complaints and a broader possibility of overlapping and convergent benefits from new therapies or new combinations of old drugs. There will be a greater emphasis on male OAB, the sexual side effects, partner benefits, risk factor modification, progression and cancer prevention, quality of life, depression/happiness/reward, hormonal issues and collateral benefits in other LUTD.

Conclusions

The epidemiological studies prove the convergence of LUTD when viewed through the lens of the current PRO and problem constructs. This convergence serves as a clear guidance to include wide ranging outcome instruments in all future studies with compounds being investigated for the treatment of LUTD. Out of these will come evidence of expected and unexpected collateral effects – or PRO. The diversity of response should open the possibility to a different business model for developing therapeutic concepts.

The simple answer to the question of what and who to treat with LUTD may come from good epidemiological and longitudinal studies and an open, commonly accepted, model of defining PRO. These should take into account a broad range of complaints and the possibility of overlapping and convergent benefits from new therapies.

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