

## WORKSHOP 13-14 September 2001

# OVERACTIVE BLADDER / URGE INCONTINENCE CRITERIA FOR ITS ACCEPTANCE FOR SELF- MEDICATION

### 1. Introduction

Overactive bladder and urge incontinence are distressing conditions for their sufferers. These conditions limit and disrupt their sufferers' everyday lives, and cause intense feelings of embarrassment, anxiety, fear, humiliation, anger, frustration and depression. The wetting accidents themselves are clearly the worst aspect of the problem, but the intense, frequent needs to urinate, the panicked bathroom searches -and the fear of not making it on time – also take their toll<sup>1</sup>.

To understand this health issue, a study based on interviews of patients affected by overactive bladder / urge incontinence was conducted<sup>13</sup>. The main findings were:

Patients described urge incontinence as an unpredictable intense urge to urinate. This can occur very frequently and often happens moments later, after these patients have just been to the bathroom.

The physical and psychological aspects of the urge incontinence have clearly had a significant impact on the patients' quality of life. They have had to curtail several activities and their lives have also changed on a more subtle level as the sufferers feel the need to plan their activities and outings according to bathroom accessibility. They also have to limit their liquid intake and monitor the times of their trips.

Even with medication, the frequency of the symptoms seems to vary anywhere from every day to several times a week to once a week.

Some of the interviewed patients in both segments said that they have been suffering from these symptoms for 11 or 12 years. Others had experienced more recent onsets in the past couple of years or within the last year.

Despite the fact that their urge incontinence is so integral to their lifestyles and their state of mind, typically this condition is an "in-the-closet" problem for many patients. These patients will not discuss about the urge incontinence with anyone other than their immediate family members. They are embarrassed and ashamed and do not want outside people to know their problem.

A significant number of patients said that they even did not discuss this problem with their doctors. They were either both too humiliated and afraid of the diagnosis and prognosis, or they did not believe that there was any form of treatment for this condition. Among those who finally did talk to their doctor, very few had actually made an appointment for a consultation on their

bladder condition, and patients brought up their condition in a visit for some other health problem.

In this context, the idea of an OTC product to help manage overactive bladder / urge incontinence – even one that only provides partial relief – is highly appealing to sufferers. Wetting accidents appear to be so distressing that even the possibility of a reduction in their number (not their complete elimination) is quite motivating for the sufferers. The additional promise that the product would lessen the frequency and intensity of urges to urinate is also highly relevant<sup>13</sup>.

## 2. Definition

In general, urinary incontinence (UI) is defined as the involuntary loss of urine that can be demonstrated objectively and which constitutes a social or hygienic problem<sup>3,4</sup>. UI occurs when the pressure within the bladder exceeds that within the urethra during the filling phase.

Overactive Bladder / Urge Incontinence is a type of UI, which is associated with a strong desire to urinate and correlates with an overactive detrusor muscle hence the term “overactive bladder”<sup>5,6</sup>. People, with overactive bladder, experience inappropriate contractions of the bladder during the storage phase of the micturition cycle. These contractions give rise to an abnormal rate of micturition - frequency, a strong desire to void - urgency, and urine loss - urge incontinence (if the desire to void cannot be suppressed). Urge incontinence is the ultimate symptom of an overactive bladder<sup>6</sup>. People with overactive bladder may also experience an abnormal rate of micturition during the night - nocturia.

Urge incontinence is then usually recognized by the abrupt sensation that urination is imminent. Patients with this type of incontinence learn the location of every toilet on their daily surroundings<sup>5</sup>.

## 3. Epidemiology of overactive bladder / urge incontinence

An extrapolation of the figures provided by Decision Resources, results in a prevalence of around 24 million people affected by overactive bladder/ urge incontinence in 2001 in 5 European countries: France, Germany, Italy, Spain and the UK.

Figures from the US, show that Overactive bladder affected more than 17 million americans<sup>10</sup>, making it more prevalent than asthma (15 million)<sup>11</sup>, osteoporosis (10 million), diabetes mellitus (7 million) or Alzheimer disease (4 million)<sup>12</sup>.

When female incontinence was classified by symptoms or urodynamics in 21 of 48 studies, urge incontinence accounted for 22% of cases in women, but it predominated in men. The incidence of urge incontinence in women increased with age and reached a maximum level among those in their sixties<sup>6</sup>.

In men, urge incontinence primarily due to a bladder irritation from benign prostate hypertrophy (BPH) was predominant (73%)<sup>6</sup>.

It is estimated that one third of people with overactive bladder have urge incontinence<sup>8</sup>. About 1 million women and 1.5 million men are affected by overactive bladder / urge incontinence in Germany<sup>9</sup>.

In general, the distribution of the three most frequent types of UI is given in the table I

Table I: Gender Distribution of Types of Urinary Incontinence<sup>2</sup>

TYPE	MEN	WOMEN
Stress incontinence	8%	49%
Urge incontinence	73%	22%
Mixed incontinence	19%	29%

Estimated figures for urinary incontinence in seven countries are given in the table II

Table II: \*UI Patient Population 2001 in 7 countries<sup>3</sup>

	France	Germany	Italy	Spain	UK	Japan	US
Total Prevalence (000s)	7852.7	12316.3	13491.3	8751.2	9127.4	14515.1	57,125.6
Percent Diagnosed	5%	5%	5%	5%	5%	5%	5%
Total Diagnosed Population (000s)	409.9	642.9	704.2	456.8	476.5	757.7	2,982.0
Percent Drug Treated	36%	36%	36%	36%	36%	36%	36%
Total Drug-Treated Population (000s)	147.6	231.4	253.5	164.5	171.5	272.8	1,073.5
Percent Compliant	25%	25%	25%	25%	25%	20%	25%
Total Compliant Population (000s)	36.9	57.9	63.4	41.1	42.9	54.6	268.4

\*Adapted from Decision Resources

#### 4. Associated Costs

The cost of treating overactive bladder / urge incontinence is considerably high for patients, families, and third-party payers. In 1995, the estimated cost of urinary incontinence in patients older than 65 years was \$26.3 billion<sup>11,29</sup>. Until recently, specialists often treated overactive bladder, but today, general and family practitioners write the majority of prescriptions for overactive bladder treatments<sup>13,14,15</sup>.

#### 5. Diagnostic of overactive bladder / urge incontinence

As mentioned-above, overactive Bladder / Urge Incontinence is a type of urinary incontinence that is characterized by a strong desire to urinate<sup>5,6</sup>. Urge incontinence is then usually recognized by the abrupt sensation that urination is imminent.

According to the National Women's Health Report, the diagnosis and treatment of overactive bladder may be made by a number of healthcare providers, including primary care physicians, nurse practitioners, geriatricians, gerontologists, urologists, gynecologists, pediatricians, neurologists, physiotherapists, continence nurses, and psychologists<sup>30</sup>.

A primary care provider can diagnose overactive bladder by taking a complete medical history and using a symptom assessment chart. One commonly conducted test is a urinalysis (a urine test to determine whether the symptoms are caused by overactive bladder, or another problem, such as a urinary tract infection or bladder stones). If the urinalysis is normal, a primary care

provider may decide to treat the patient or refer him or her to a specialist for further examination solely on the basis of the symptoms. For the majority of patients, however, referral is not necessary<sup>30</sup>.

In some patients, a focused physical exam of the lower urinary tract, including neurologic assessment of the legs and perineum, may also be needed. In addition, the patient can be asked to complete a bladder diary (a written record of his or her liquid intake, amount and frequency of urination, and sense of urgency) for a few days to obtain more information about symptoms. If, after these steps are taken, a definitive diagnosis has still not been made, the patient may be referred to a specialist for a urodynamic assessment. This test will provide information about the pressure/ volume and pressure/flow relationships within the bladder. Measurement of the detrusor pressure during cystometry is used to confirm a diagnosis of detrusor overactivity. In normal healthy adults, the detrusor pressure is low (no phasic contraction) during bladder filling until the cystometric capacity is reached. However, in people with detrusor instability or detrusor hyperreflexia, the detrusor pressure pattern shows that the waves of pressure increased in amplitude as the bladder filled with urine. Sometimes these waves result in leakage<sup>16</sup>.

In some patients, it may also be necessary to use imaging techniques, such as ultrasound, X-ray contrast studies, or computerized tomography. An additional cystoscopy may also be needed<sup>30</sup>.

In a qualitative research study done in patients suffering urine incontinence, it was observed that although some women at first did not seem to differentiate between urge incontinence and stress incontinence (urine leakage when they laughed, coughed or sneezed), with probing it became evident that, in fact there was a clear distinction. Leakage related to coughing or laughing, even though annoying and embarrassing, is not accompanied by the same panic and anxiety related to urge incontinence<sup>13</sup>.

## **6. Differential diagnosis (UI)**

Urge Incontinence has to be differentiated from other conditions such as:

### **6.1 Other types of urine incontinence**

#### **6.1.1 Stress incontinence**

Stress incontinence arises as a result of a defect in the urethral closure mechanism. The primary defect is essentially the failure of the external urethral sphincter to counterbalance that increases in intra-abdominal pressure, either as a result of damage to its muscle fibers or to its nerve supply. Weakness of the urethral support (hypermobility) and neurological damage to the pelvic floor, bladder neck or urethra predispose individuals to this condition<sup>16,17,18</sup>

Sufferers of stress incontinence can identify this condition by the fact that it produces leak of small volumes of urine following actions such as laughing, coughing, sneezing, lifting, jumping and running, all of which produce sudden increases in intra-abdominal pressure<sup>16</sup>.

Stress incontinence commonly occurs in women who have had a number of children, possibly as a result of damage to the pelvic floor during vaginal delivery. However, women who have never had children, however, may also suffer from this condition.

Stress incontinence is estimated to affect approximately 25% of women with urinary incontinence and is very rare in men<sup>16</sup>.

Surgery is the most effective treatment with a cure rate of 75 to 85%<sup>28</sup>.

### **6.1.2 Mixed incontinence**

This term describes people who suffer from both urge incontinence (caused by overactive bladder) and stress incontinence. In individual cases one type may be predominant<sup>16,17,18</sup> and will generate the typical clinical feature of either overactive bladder/urge incontinence or stress incontinence. It has been estimated that between 33% and 55% of women who are incontinent suffer from mixed incontinence.

### **6.1.3 Overflow incontinence**

Overflow incontinence is associated with increased volume of residual urine and an impaired contractile capacity of the bladder. In the majority of cases, this condition occurs secondary to benign prostatic hyperplasia (BPH) with outlet obstruction, and is consequently more prevalent in men than in women. Overflow incontinence also occurs in women as a result of a weak detrusor muscle<sup>16,17,18</sup>.

The absence of the strong desire to urinate may be useful for patients to differentiate overflow incontinence from urge incontinence.

### **6.1.4 Post-micturition dribble**

Post-micturition dribble is identified by the loss of small amounts of urine after voiding is completed. It occurs mostly in men. Post-micturition dribble is explained by leakage of urine trapped in the urethra at the end of voiding<sup>16</sup>.

Sufferers can also differentiate post-micturition dribble from urge incontinence by the absence of its key sign, the strong desire to urinate.

### **6.1.5 Urinary fistula**

In women, a urinary fistula is an abnormal connection between the epithelium of the ureter, bladder, or urethra and the epithelium of the uterus or vagina. Urinary fistulas are recognizable because they cause continuous urinary incontinence that is unrelated to the urge to void or physical activity. Urinary fistulas may arise after surgical trauma (e.g. after a hysterectomy, Caesarian section, or vaginal repair), obstructed labor or in association with pelvic malignancy and radiation therapy<sup>16</sup>.

### **6.1.6 Urinary tract infection (cystitis)**

The terms urinary tract infection (UTI), bacterial cystitis and cystitis are used interchangeably to describe bladder infections, if verified by urinalysis and/or urine culture. Patients who suddenly experience frequency and urgency accompanied by painful urination, abdominal pain, fever and other symptoms<sup>19</sup> will be able to suspect that an infection rather than increased frequency and urgency due to an overactive bladder

### **6.1.7 Bladder stones / bladder tumors**

Bladder stones also produce frequent urge to urinate, but other signs like interruption of the urine stream, inability to urinate in certain positions, blood in the urine, abdominal pain or discomfort in the lower abdomen and pain or discomfort in the penis<sup>20</sup>, help to establish the differential diagnosis.

Bladder tumors usually do not cause any symptoms and remain unnoticed until an episode of bleeding into the urine occurs. After an episode of bleeding into the urine, the patient should undergo an evaluation by a urologist<sup>21</sup>.

### 6.1.8 Interstitial cystitis

Interstitial cystitis (IC), one of the chronic pelvic pain disorders, is a condition resulting in recurring discomfort or pain in the bladder and the surrounding pelvic region. The symptoms of IC vary from case to case. People may experience mild discomfort, pressure, tenderness, or intense pain in the bladder and surrounding pelvic area. Symptoms may include an urgent need to urinate (urgency), frequent need to urinate (frequency), or a combination of these symptoms. Pain may change in intensity as the bladder fills with urine or as it empties. IC is far more common in women than in men. 90% of sufferers are women. These patients may be unable to work and impossible for them to have sex comfortably. Fifty per cent are unable to drive a car comfortably<sup>10</sup>.

## 7. Treatment of Overactive Bladder / Urge Incontinence

Once a healthcare provider has made a diagnosis of overactive bladder, several treatment options are available, depending on the needs of the patient. The Agency for Health Care Policy and Research Panel on Incontinence, recommends that treatment should first begin with the least invasive therapies, which often means bladder retraining and medication. Bladder retraining programs, often used in conjunction with medication, have also provided good results for patients. These programs are based on gradually increasing the time between visits to the bathroom<sup>30</sup>.

Pharmacological therapy is currently the mainstay of treatment for overactive bladder<sup>29</sup>. In people with overactive bladder the detrusor muscle contracts involuntarily as the bladder fills, causing the pressure within the bladder to exceed that within the urethra, and leakage of urine occurs. It is generally agreed that the contractions of the detrusor muscle during normal voiding, and the uncontrolled contractions associated with overactive bladder, are both mediated primarily by stimulation of cholinergic muscarinic receptors<sup>7,15,22</sup>. Consequently, antimuscarinic drugs, that block these receptors, have become well established in the treatment of overactive bladder.

All anticholinergic drugs are contraindicated in patients with documented untreated narrow-angle (but not wide-angle) glaucoma<sup>23</sup>.

### 7.1 Oxybutynin.

Oxybutynin acts as both an anticholinergic agent and a smooth muscle relaxant. The recommended dosage is 2.5 to 5 mg orally three or four times a day<sup>23</sup>.

Side effects, including dry mouth, were noted in all the clinical trials of conventional oxybutynin, and severity increased as the dosage did.

The FDA has recently been approved a controlled-release formulation of oxybutynin for marketing. This new formulation is a pill with an osmotic pump that steadily delivers the drug over a 24-hour period<sup>23</sup> and is supposed to reduce dry mouth, the most frequent adverse event with anticholinergic agents.

Long-acting oxybutynin (Ditropan XL; Alza Corporation, Mountain View, California) uses a slow-release technology known as the oral osmotic (OROS) technology. The OROS delivery technology osmotically delivers steady-state serum levels over a 24-hour time frame, which avoids the peaks and troughs associated with the intermittent dosing schedules of the immediate-release formulation (zero-order kinetics). Plasma levels rise over a 4- to 6-hour period and then, remain in steady-state for a 24-hour period after oral ingestion. Stable plasma concentrations are achieved by day 3 of continuous ingestion. Drug metabolism is not affected by dietary intake<sup>14,15,23,24</sup>.

The primary metabolic pathway of oxybutynin chloride is the cytochrome P3A4 system, and the half-life of oxybutynin chloride is approximately 3 hours. The half-life of the XL formulation is 12 to 13 hours. The primary metabolite of oxybutynin is N-desethyl oxybutynin. Both parent and metabolite have antimuscarinic activity; however, the metabolite is thought to be the primary cause of adverse effects associated with oxybutynin ingestion. After oral ingestion of immediate-release oxybutynin, levels of metabolite increase to a level 6-fold higher than the parent compound. Newer delivery methods have attempted to decrease these high serum levels of metabolite<sup>7,22,24</sup>.

## 7.2 Tolterodine

Tolterodine; (Pharmacia & Upjohn, Kalamazoo, Michigan) is a muscarinic receptor antagonist that was approved for marketing by the FDA in 1998. In a recent clinical trial, patients who received tolterodine reported fewer episodes of dry mouth than those who received conventional oxybutynin<sup>14,15,23,24</sup>.

Tolterodine shows to be more specific for the M<sub>2</sub> receptor. This drug also has less M<sub>3</sub> receptor activity with a direct correlation to lessen dry mouth. Bioavailability after oral administration is variable, which may reflect differences in inter-individual differences in hepatic metabolism. The half-life of tolterodine is approximately 4 hours. Time to peak therapeutic effect is 2 hour, and >90% of the drug is protein bound. The primary metabolic pathway is cytochrome P3A4 and cytochrome P2D6. The role of any degradation products in the overall safety and efficacy profile of tolterodine is unknown; however, the metabolite PNU 20057 has been shown to have direct detrusor effects. This drug may demonstrate some organ selectivity in that it produces less xerostomia than immediate-release oxybutynin; however, this may be more reflective of M<sub>3</sub> receptor affinity differences between organs than global receptor effects<sup>7</sup>.

The standard dose of tolterodine is 1-2 mg twice daily, although clinical trials have investigated doses as high as 4 mg twice daily. Higher doses (4 mg) have been reported to be associated with increased rates of urinary retention and dry mouth rates approaching 56%. Rates of side effects were not noted to be higher in poor or extensive metabolizers of tolterodine, in grouped analysis, suggesting the overall tolerability of the formulation at lower doses. In a pooled analysis, evaluating 4 trials over a 12-week study time frame with 1,120 patients included, that there was reduced dry mouth severity associated with tolterodine and essentially equal reductions in frequency and incontinence episodes between tolterodine and immediate-release oxybutynin. Clearly, as tolterodine levels were increased, better efficacy was obtained, albeit with greater side-effect profile<sup>7</sup>.

A recent large-scale clinical trial demonstrated again the efficacy and tolerability of tolterodine in 1,022 patient's urgency, frequency, and urge incontinence. Treated patients showed a 46% reduction in urge incontinence episodes compared with placebo (P=0.0005), with significant improvements noted in frequency (reduced by 15%) and pad usage (36% reduction), with substantial improvement in volume voided per micturition (21%). No significant difference between treated or placebo groups were noted for patients withdrawing due to tolerability concerns, although 40% of patients perceived a substantial benefit from treatment (compared with 22% for placebo). The only tolerability concern that significantly segregated tolterodine from placebo was that 30% of actively treated patients experienced dry mouth (18% mild severity) compared with only 8% of placebo-treated patients<sup>7</sup>.

A new once a day formulation (LA) for tolterodine has recently been launched in the U.S. Studies and have demonstrated the effectiveness of tolterodine LA. Significantly more patients taking once-daily tolterodine LA reported improvements in their overall bladder condition compared with those treated with placebo, and tolterodine LA produced a significantly greater reduction in the number of incontinence episodes per week than placebo. In addition, tolterodine LA significantly reduced bathroom visits compared with the placebo group<sup>7,27</sup>.

### 7.3 Alternative agents

Desmopressin in oral and intranasal spray formulations were recently approved for bedtime-use to treat detrusor instability and nocturnal enuresis. Also, phase III trials have been started to test its effect given at bedtime in men who have benign prostatic hyperplasia and in elderly persons, who generally experience nocturia more often than younger persons<sup>23</sup>.

Capsaicin in 30% alcohol administered intravesical has shown to reduce UI significantly compared with placebo in patients with neurogenic hyperreflexic bladder<sup>23</sup>.

More agents that have been used in the treatment of overactive bladder are listed in the table III.

**Table III: Other pharmacologic agents for overactive bladder<sup>24</sup>**

Agent	Type/Class	Dose	Comment
Propantheline bromide (Pro-Banthine <sup>†</sup> )	Quaternary amine	15-30 mg tid	-50% reduction in urge incontinence -Pure anticholinergic, significant gut side effects
Hyoscynamine sulfate (Levsin <sup>±</sup> , Cystospaz <sup>§</sup> )	Muscle relaxant	0.125 mg qid	-Weak anticholinergic effects, similar to belladonna alkaloids
Dicyclomine hydrochloride (Bentyl <sup>†</sup> )	Muscle relaxant	20 mg tid	-Direct smooth muscle relaxant, with antimuscarinic activity -Reported improvement rates up to 73%
Flavoxate hydrochloride (Urispas <sup>®</sup> )	Muscle relaxant	100-200 mg tid/qid	-Tertiary amine with very weak anticholinergic properties
Imipramine hydrochloride (Tofranil <sup>†</sup> )	Tricyclic antidepressant	10-50 mg tid	-Central and peripheral effect -Also sedative and antihistaminic -31% cure rate and 2%-77% urge reduction rate
Doxepin (Sinequan <sup>#</sup> )	Tricyclic antidepressant	50 mg	Same as above
Terodiline	Calcium channel blocker	25 mg bid	-Direct smooth muscle contractility reduction -Torsade de pointes arrhythmias
Pinacidil, AD6169	Potassium channel openers	Variable	-Withdrawn from market -Smooth muscle relaxant -Side-effect profile complicated by dizziness and edema
Flurbiprofen, indomethacin	Prostaglandin inhibitors	Variable	-Anti-inflammatory -Muscle relaxant

\* Watson Laboratories, Corona, California

† Roxane Laboratories, Columbus, Ohio.

- § Schwarz Pharmaceuticals, Milwaukee, Wisconsin.
- ° Polymedica, Woburn, Massachusetts.
- º Alza Pharmaceuticals, Mountain View, California.
- ¶ Novartis, East Hanover, New Jersey.
- # Pfizer, New York, New York.

## 7.4 Developmental agents

Trospium is administered 3 times a day, with doses including 5, 15, and 30 mg. The half-life is variable, 5 to 21 hours, with the majority of the drug undergoing renal excretion without molecular degradation. Only 6% of ingested drug is bioavailable, that parallels levels seen with other tertiary amines and may be reflective of intestinal absorption differences with this drug. In a study of 2,647 evaluable patients treated for 30 days with trospium, the frequency was reduced by 40% and urge symptomatology by 87%. Only 28 adverse events were reported in this population<sup>24</sup>.

Additionally, trospium is well tolerated with intravesical administration and appears to be only minimally absorbed systemically. This finding may indicate a substantial direct muscolotropic effect. This parallels the muscolotropic activity seen with intravesical oxybutynin<sup>24</sup>.

Another selective antimuscarinic agent in development is darifenicin. This drug is an M<sub>3</sub> – selective antagonist, with an 11-fold higher affinity for this receptor compared with the M<sub>2</sub> receptor. In vitro, it appears to be selective for detrusor receptors, and specifically in canine and rodent models has clear affinity for bladder over salivary gland. However, this selectivity is not as profound in other mammalian species. Currently ongoing clinical phase 2 trials may better reveal the human tolerability/efficacy profiles. In a small study of 18 patients treated with 10 mg of darifenicin, improvement in urodynamic parameters was seen. Other data indicate an improvement in quality-of-life parameters after acute treatment with darifenicin<sup>24</sup>.

Clinical trials are either ongoing or contemplated for NK-receptor antagonists, specific muscarinic subtype agonists/antagonists, and racemic oxybutynin<sup>9</sup>. Pooled clinical studies submitted to the US Food and Drug Association (FDA) revealed an 83% - 90% reduction in urgency incontinence episodes associated with ingestion of this drug<sup>24</sup>.

Duloxetine<sup>23</sup> (phase II), is a serotonin and norepinephrine reuptake inhibitor. It is in phase II and phase III trials now for treatment of both urge and stress incontinence and could be available in 2 or 3 years.

## 8. Quality of life related to Urge Incontinence

Surveys of UI' patients show that they are most bothered by the interruption of their daily activities and not by the daily number of used pads and by the number of times they are awakened at night. Patients put up with many problems but find it intolerable when they cannot go shopping, meet with friends, or go out to dinner<sup>5</sup>.

Only a small percentage of patients with urinary incontinence (UI) receive treatment for this problem. One reason is the discomfort physicians often feel in dealing with UI<sup>23</sup>.

The experience of urge incontinence typically begins with a sudden, strong urge to urinate. These urges are often unpredictable, and can occur very frequently – even immediately after a previous trip to the bathroom. Once an urge strikes, a patient generally has only a very brief time – a few minutes or less – to find a bathroom. When the patient can not get to a bathroom on time, a wetting accident occurs<sup>4</sup>.

The patients experience wetting accidents anywhere from occasionally to several times a week or more. A few claimed to never have experienced a full wetting accident. However, the sudden need to urinate are much more frequently – often several times a day<sup>1</sup>.

Experiencing urge incontinence has forced sufferers to alter their lifestyles, often drastically, in order to manage the condition and reduce the frequency of accidents. Patients have reported:

- Reducing the time they spend away from home
- Planning their activities and outings where there exists bathroom accessibility
- Giving up much-enjoyed activities (e.g. visiting the theater, going horseback riding, taking long road trips)
- Making frequent “preventative” trips to the bathroom, even when they don’t feel the need to urinate
- Using less-than-clean public bathrooms, and even cutting lines in order to avoid an accident.
- Women using the men’s room in order to avoid an accident
- Limiting intake of liquids
- Avoiding wearing light colored clothing
- Carrying a clean underwear or even an entire change of clothes, at all times<sup>1</sup>

Beyond the physical symptoms themselves and the lifestyle changes they require, urge incontinence has an extreme emotional impact. Sufferers report intense feelings of embarrassment, fear, anxiety, humiliation, anger, frustration and depression. They are constantly frightened that they might have an accident in public – that people will detect a urine smell on them, notice stains on their clothing, or otherwise find out about their problem. Some speak of feeling old, disabled, out of control or their bodies, and wonder how the problem will progress as they grow older<sup>1</sup>.

The wetting accidents themselves are clearly the most distressing aspect of urge incontinence. However, importantly, it seems that the frequent urges – and the panicked rush to the bathroom that they often prompt – are also highly disruptive and carry their own emotional toll. In fact, women who reported experiencing only occasional wetting accidents or none at all were clearly heavily impacted by this problem<sup>1</sup>.

Apparently because of the lifestyle impact and the emotional issues surrounding urge incontinence, sufferers typically rank the problem as the #1 or #2 health concern affecting them – even ahead of serious diseases such as diabetes, arthritis, asthma or high blood pressure<sup>1</sup>.

Most of the prescription users, and many of the non-users, wear some sort of pad, panty liner or diaper to protect themselves in the event of an accident. However, for all but the most severe sufferers, these products appear to serve as a back-up only – they make every attempt to get to a bathroom on time, and use the pad or diaper only if absolutely necessary<sup>1</sup>.

In addition, some of the female patients appeared to be using too light of a product to provide the degree of protection they need (e.g. a sanitary napkin in place of an incontinence pad or diaper). As a result, an accident is still likely to result in (perhaps visible) wetness and staining<sup>1</sup>.

## **9. The patient’s view point on the use of Medications for Urge Incontinence**

All of the users of prescription medications for urge incontinence reported some improvement in their condition as a result of using these medications. Most were quite satisfied by even a partial reduction in their symptoms<sup>13</sup>.

The patients typically had seen a significant reduction in the number of wetting accidents they experienced (most estimated between 40% and 80%), though only a couple had eliminated these accidents entirely.

Furthermore, most had experienced a reduction in the frequency and intensity of the urge to urinate, giving them a greater chance of making it to the bathroom in time.

As a result of these improvements, the patients had been able to resume activities they had previously given up, and emotionally felt more confident, and less anxious and panicked about their symptoms.

Virtually all of these prescription users had experienced some degree of dry mouth as a result of using the medication, but most agreed it was an acceptable trade-off for the relief of their symptoms<sup>13</sup>.

Sufferers of urge incontinence found the concept of an OTC remedy to be highly appealing<sup>13</sup>.

In particular, non-users of prescription medications for urge incontinence were often unaware that this problem could be treated with medication, and were quite eager to try one if it were available.

Upon prompting, most sufferers clearly understood that this product would provide only partial relief, and nonetheless found the proposition compelling<sup>13</sup>.

Apparently, wetting accidents are so distressing that even the possibility of a reduction in their number (not their complete elimination) is quite motivating.

Furthermore, some of these users inferred that the product would also reduce the number of times they got the strong need to urinate, also a highly relevant benefit.

Most of the interviewed people felt that the side effect of dry mouth would be one they could easily live with<sup>13</sup>.

## **10. The role of patient organizations**

The aims of organizations like continence foundations in several countries are to help people with incontinence and to improve public understanding of the condition.

Their main areas of activity are:

Advice - providing information and advice, not only to people who have problems of bladder control and their relatives and careers but also to those professionally concerned

Awareness - raising public awareness of incontinence and promoting media coverage

Advocacy - promoting better policies for continence services and campaigning for continence to be given a higher priority in NHS and other budgets<sup>25,26</sup>

## **11. Rationale for OTC switch**

Unmet consumer need is evident in overactive bladder / urge incontinence. Patients are suffering in silence because they feel embarrassed even to inform the problem to their doctors. Close to a quarter (23%) have never discussed the condition with their doctor<sup>13</sup>. Three in ten (31%) of women with urge incontinence have not discussed their condition with anybody.

A significant percentage of persons do not seek help because they are embarrassed or because they are not aware that help is available attesting to the largely unmet consumer need.

Quality of life is negatively impacted by this condition. Close to half (46%) of sufferers have had to change their lifestyle in order to deal with overactive bladder / urge incontinence. One in five women have been forced to entirely eliminate some activities<sup>13</sup>.

50% of patients call their condition a “major problem” or “always bothersome.” More than half say losing control of bodily functions would have the greatest impact on their feelings of attractiveness and sexuality – two times as many who say the inability to be physically active, and four times as many who say changes in physical appearance would have the greatest impact<sup>13</sup>.

A relatively small percentage of women are aware of the latest innovations in urinary leakage treatments. A much larger number know only of the traditional options<sup>13</sup>. News media (39%), newsletters on incontinence (34%), Physician (25%), product advertising (15%), books on the subject (13%), friends (9%) and family members (4%), are the sources where patients usually first hear about new treatment methods<sup>13</sup>.

Urge incontinence can be readily discernable by the consumer. Although a research study has shown that some sufferers at first did not seem to differentiate between urge incontinence and stress incontinence (urine leakage when they laugh, cough or sneeze), with probing it became evident that in fact there is a clear distinction.

Furthermore, it is reasonable to expect that the consumer can differentiate “urge” incontinence from “stress” incontinence when labeling information is provided and that it would emphasize urge incontinence as a condition associated with a sudden desire to urinate that may result in loss of urine. An adequate labeling will also exclude subjects with other conditions from self-selecting for OTC treatment of overactive bladder / urge incontinence.

Oxybutynin or tolterodine as discussed previously, have an efficacy and safety profile that lends their self to OTC use. The safety is additionally borne out in their use as prescription products.

In summary, overactive bladder / urge incontinence can be switched to an OTC manageable condition due to:

- Highly prevalent condition that affects millions of people and negatively impacts their quality of life
- The need to help patients who suffer in silence and do not inform their doctors about their condition because of embarrassment
- Condition has proven to be self recognizable by the consumer
- Delay in its diagnosis does not present an overt health risk to consumer
- Oxybutynin and tolterodine, drugs commonly used for the treatment of this condition, have demonstrated adequate efficacy and safety profile for OTC use.

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