

Anti-diuresis in the management of daytime urinary incontinence

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Abstract

Urinary incontinence and lower urinary tract dysfunction, whilst not life threatening conditions, remain an important cause of morbidity in women and are responsible for significant impairment of quality of life. Drug therapy is often used to treat women who complain of urgency and urge incontinence and has an emerging role in the management of stress urinary incontinence. However, bothersome side effects are known to affect compliance and therefore compromise efficacy, making longterm drug therapy unpopular.

The principle aim of this thesis is to assess the role of antidiuresis in women complaining of daytime urinary incontinence and also to examine its role as a 'designer therapy' which women can choose to use as, or when, required. In addition both the patients' and clinicians' attitudes towards treatment have been studied to clarify the meaning of 'cure', and to determine treatment acceptability, overall outcome and patient satisfaction.

In the first study the patients' concept of cure is explored as well as their expectations regarding treatment and outcome. The second study examines cure from the clinician's perspective in addition to reviewing outcome measures in the clinical and research settings. Finally in the third study the use of desmopressin in women complaining of daytime urinary incontinence is reported.

1. What do women want? Interpretation of the concept of cure

Rationale

Urinary incontinence and lower urinary tract dysfunction are common distressing conditions that are known to adversely affect quality of life (Kelleher *et al.*, 1997). In a large community based study of 27 936 women in Norway 25% of women complained of urinary leakage of which 7% regarded their incontinence as severe (Hannestad *et al.*, 2000). Further epidemiological studies have demonstrated a significant effect on quality of life; those women with urge incontinence and mixed incontinence having a significantly poorer quality of life when compared to those with stress incontinence although overall only 6% had sought medical advice and hence a solution or 'cure' to their problems (Simeonova *et al.*, 1999).

The grammatical definition of cure is a 'restoration to health or good condition' although in the clinical setting may be defined in a number of different ways. Subjective cure is the resolution of reported clinical symptoms whereas objective cure describes the outcome of repeat laboratory testing. Whilst symptomatic improvement is clearly the aim of intervention in lower urinary tract dysfunction this provides a qualitative rather than quantitative assessment and is more difficult to measure. Consequently objective outcome measures are considered to be more robust and are used as an outcome measure in many clinical studies. At present there is no consensus of opinion regarding which should be thought of as more important although guidelines have been published (Mattiasson *et al.*, 1998. Lose *et al.*, 1998). This study was designed to test the hypothesis that there is no difference amongst women regarding their understanding of 'cure' and their expectations following treatment of lower urinary tract dysfunction.

Objectives

Primary objective

The primary objective of this study was to determine what women perceive as 'cure' and to evaluate which urinary symptoms are troublesome and which are acceptable following treatment.

Secondary objective

The secondary objectives were to assess the acceptability with regard to management of lower urinary tract dysfunction and to investigate if there is a relationship between symptom severity and expectations regarding outcome.

Patients and Methods

Study Population: Women were recruited prospectively from a urodynamic clinic in a tertiary referral urogynaecology unit. All complained of troublesome lower urinary tract symptoms and had been referred, by general practitioners or consultants from other hospitals for further investigation and management.

Inclusion Criteria: All consenting English-speaking women referred to the urodynamic clinic for investigation of lower urinary tract symptoms were eligible for inclusion in the study.

Exclusion Criteria: Women were excluded from the study if they met one of the following exclusion criteria: (1) 'Cure' questionnaire not completed satisfactorily, (2) Kings Health Questionnaire not completed satisfactorily, (3) Withdrawal of verbal consent.

Methods

Prior to urodynamic studies objective assessment of lower urinary tract symptoms was performed using the King's Health Questionnaire (KHQ) (Kelleher *et al.*, 1997) whilst subjective assessment of expectations regarding 'cure' was carried out using a specially designed questionnaire based on structured qualitative clinical interview. All patients with lower urinary tract symptoms were eligible for inclusion.

The questionnaire was divided into four sections:

1. The first asked which lower urinary tract symptoms would be acceptable following treatment. Three responses for each symptom were available (yes / probably / no).
2. The second asked women to specify themselves which particular symptom they found most troublesome
3. The third asked what they felt would be a good (but realistic) outcome of treatment.

4. The final question asked which treatments they would find acceptable and be willing to undertake.

The questionnaire generally took five minutes to complete and was given to patients immediately prior to urodynamic studies and before they had seen a clinician.

Validation of Cure Questionnaire

In order to measure the test-retest reliability a second cure questionnaire, with an accompanying letter and a reply paid envelope was posted and completed by women 2 weeks following initially completing the questionnaire. A short interval between responses was chosen to ensure that their symptoms and opinions remained unchanged. The responses of the two questionnaires were then analysed using a Cronbach alpha (SPSS, Chicago, USA). A Cronbach alpha of > 0.7 has been recommended as acceptable. For an unknown population in order to show a one standard deviation difference with 80% power at 0.05 significance 35 patients are required.

In total 50 questionnaires were sent out and 39 were returned completed correctly, giving a response rate of 78%. Overall the mean Cronbach alpha for the questionnaire was 0.797 indicating acceptable reproducibility.

Statistical Methods

'Cure' questionnaire results and urodynamic diagnosis were recorded and a database compiled. The KHQ QoL questionnaire was scored using the scoring system described. The database was then checked for accuracy and analysed using the Statistical Package for Social Sciences (SPSS, version 10 for Windows). Correlation of QoL scores, symptom acceptability and treatment acceptability was performed using Kendall's tau b method. Observed differences were considered to be significant when p was less than 0.05.

Table 1. — Urodynamic diagnosis of the patient population.

Urodynamic Diagnosis	Cases (%)
Urodynamic stress incontinence	24%
Detrusor overactivity	20%
Mixed incontinence	15%
Voiding difficulties	4%
Sensory urgency	3%
Normal	17%
No diagnosis recorded	17%

Table 2. — Expectations following treatment.

Complete cure of all bladder symptoms	17%
A good improvement so they no longer interfere with your life	43%
Being able to cope better so your life is affected less	13%
Any improvement in your bladder symptoms, no matter how small	10%

Results

In total 100 consecutive fit, healthy, women were recruited over a two-month period. The mean age was 47.5 years (range: 20-73 years) and mean duration of symptoms 6.0 yrs (range: 6 mths-40 yrs). The urodynamic diagnoses are shown below (Table 1).

Expectations following treatment

The results concerning overall expectations of treatment are shown below (Table 2).

Acceptability of symptoms

Patients were also asked what symptoms they would be content to accept following treatment and these are shown below (Table 3).

Acceptability of treatments

Finally patients were asked which interventions they would find acceptable as a treatment for their lower urinary tract symptoms. These results are shown below (Table 4).

Quality of Life Assessment and Expectations of Outcome

Analysis of QoL scores using the King's Health Questionnaire (KHQ) was performed for each domain and these results are shown below (Table 5). A higher score is suggestive of increasing impact on quality of life.

Further analysis using Kendall's tau b method showed there was no correlation between QoL score and acceptability of symptoms ($r = -0.031$; $p = 0.756$) or QoL scoring and acceptability of treatment ($r = 0.127$; $p = 0.245$). Sub group analysis by urodynamic diagnosis and duration of symptoms did not alter these findings.

Discussion

This was the first study to address patients' attitudes towards the management of lower urinary tract symptoms and outcome of treatment. Overall patients would appear to have realistic expectations regarding 'cure' of urinary symptoms, with the majority of women hoping for a good improvement so that their quality of life improves. Whilst 17% of women hoped for a complete cure of all their symptoms it is interesting that 10% hoped for any improvement, no matter how small. This may reflect our population where many women were referred having had previous failed treatment.

Acceptability of Symptoms

When considering symptoms following treatment of lower urinary tract dysfunction it is perhaps not surprising that the majority of women find large or frequent episodes of urinary leakage unacceptable. However, small or occasional episodes of leakage on

Table 3. — Acceptability of symptoms following treatment.

	Yes	Probably	No
Never ever leaking no matter what you do	63%	22%	13%
Occasional small leak on coughing or sneezing	22%	43%	33%
Occasional small leak on strenuous exercise	29%	42%	27%
Occasional large leak on coughing or sneezing	8%	9%	78%
Frequent small leaks on coughing or sneezing	14%	22%	61%
A sudden urge or need to pass water (no leaking)	26%	34%	40%
Occasionally leaking before reaching the toilet	15%	32%	52%
Having to pass water very often during the day	26%	39%	34%
Having to get up once at night to pass water	36%	37%	24%
Having to get up twice or more at night to pass water	15%	21%	63%
Occasionally having to wear panty liners 'just in case'	20%	38%	38%
Occasionally having to wear pads 'just in case'	12%	24%	61%
Having to continue to wear pads most of the time	9%	5%	85%
Leaking during sexual intercourse	7%	9%	79%

Table 4. — Acceptability of treatments.

	Yes	No
Pelvic floor exercises for 6 months	60%	26%
Pelvic floor exercises for life	41%	44%
Regular drugs for life	14%	69%
Drugs to take as needed	51%	32%
Major operation (85% cure; 2% risk of self catheterising)	23%	57%
Minor operation (85% cure; 2% risk of self catheterising)	38%	43%
Clinic procedure (60% improvement; no long term risk)	57%	24%
Long term catheter	3%	79%
Learning to self catheterise	11%	73%

strenuous exercise are seen to be less problematic suggesting that women develop coping strategies to manage mild stress incontinence, such as bracing of the pelvic floor musculature and perhaps avoidance of provocative manoeuvres. Irritative urinary symptoms such as urgency and urge incontinence are not so well tolerated and this would concur with previous studies showing that there is greater quality of life impairment in women with a diagnosis of detrusor overactivity (Kelleher *et al.*, 1997). Day-time urinary frequency and voiding once at night seem to be tolerated relatively well although nocturia was unacceptable to the majority of women. These findings are in agreement with previous work reporting nocturia to be bothersome in 69% of women (Swithinbank *et al.*, 2000) and the leading cause of sleep disturbance (Middelkoop *et al.*, 1996) in adults.

When considering the use of continence products most women would find the use of a small pad or panty liner acceptable although they do not want to have to wear pads on a continuous or frequent basis. Unsurprisingly the vast majority of women would find it difficult to tolerate intercourse incontinence.

Acceptability of Treatment

When considering treatment of lower urinary tract dysfunction over half of women considered a short

course of pelvic floor exercises acceptable although substantially fewer would wish to continue over a long time period. Equally regular drug therapy was found to be unpopular although medication to be used as required was acceptable to half of the women questioned. These findings would agree with a follow-up study of women with detrusor overactivity in which only 5.5% were cured of their urinary symptoms and only 18.2% of women continued drug therapy in excess of six months (Kelleher *et al.*, 1997).

With regard to surgical intervention it was interesting, although not surprising, to find that less invasive surgery was more attractive, even if this meant a potential 'trade off' in terms of lower success rates. This would be in keeping with the general trend to less invasive surgical techniques leading to a shorter hospital stay and earlier return to work. Although not mentioned by name in the questionnaire the operations referred to were a Burch colposuspension, tension free vaginal tape (TVT) and injectable bulking agent. Success and complication rates were approximated on the basis of the available literature and are in line with our own results where these three techniques are offered. It was not surprising that as a last resort longterm catheterisation or clean intermittent catheterisation was universally unpopular.

An additional analysis was performed to examine any correlation between QoL impairment and overall

Table 5. — King's Health Questionnaire Scores (KHQ).

Domain	Median Score	5 th /95 th Confidence Intervals
General Health Perception	25.0	0.0 – 75.0
Incontinence Impact	66.7	0.0 – 100.0
Role Limitations	50.0	0.0 – 100.0
Physical Problems	50.0	0.0 – 100.0
Social Limitations	22.2	0.0 – 100.0
Physical Relationships	33.3	0.0 – 100.0
Emotions	44.4	0.0 – 100.0
Sleep and Energy	50.0	0.0 – 100.0
Severity Measures	60.0	0.0 – 100.0

expectations regarding treatment outcome. We had postulated that those women with more severe urinary symptoms and a greater degree of QoL impairment would be content with any degree of improvement and would be willing to accept a greater range of management options. This was not found to be the case. Equally there was also no correlation between acceptability of outcome and duration of symptoms.

Study Design and Appraisal

When considering the methodology of this study there are some possible weaknesses and criticisms. The sample size of one hundred consecutive women is relatively small although this sample was representative of the local population attending for urodynamic studies. When considering sample size we were unable to perform a power calculation as this was the first study, as far as we are aware, to address patients attitudes to cure. However, despite these weaknesses this study has provided an insight into the patients' concept of cure and has also provided a model for a further questionnaire based study investigating the clinicians' attitudes towards cure.

Conclusion

This was the first reported study addressing the concept of 'cure' used and examining patient's attitudes towards the treatment they receive and the outcome of that treatment. Our results support those of previous QoL studies and reiterate the importance of the definition of 'cure' when considering outcome in both the clinical and research settings. These findings may prove helpful when counselling patients regarding management of their lower urinary tract symptoms in addition to continuing the debate regarding the concept of 'cure'.

2. The Clinician's Perception of Cure

Rationale

The questionnaire-based study of patients reported in **section one** has demonstrated that there is a considerable variation in patients' interpretation of cure and that this does not depend on symptom severity. Previous studies have also found a difference between clinicians and patients in the perception of outcome following continence surgery (Black *et al.*, 1997) with clinicians tending to be more optimistic when considering success.

Whilst such 'bias' in subjective evaluation is well documented there is a paucity of data regarding symptoms and bothersomeness following treatment

of lower urinary tract pathology. Equally there is currently little information regarding clinicians' perceptions of cure and whether their perception of bothersome symptoms is similar to that of the patient.

Assessment of outcome may be either subjective or objective. Although at present there is no consensus of opinion regarding the best method of outcome assessment, guidelines have been proposed by the International Continence Society (Mattiasson *et al.*, 1998; Lose *et al.*, 1998), the Urodynamics Society (Blaivis *et al.*, 1997), the American Urological Association (Blaivis, 1998) and the World Health Organisation International Consultation on Incontinence (ICI, 2000). Since incontinence is multidimensional any measure of the outcome of treatment should attempt to evaluate the patient's and clinician's observations in addition to both objective assessment and quality of life evaluation. Consequently at present there is no single outcome measure that is adequate to assess treatment of lower urinary tract dysfunction. This study was designed to test the hypothesis that there is no difference amongst clinicians regarding their understanding of 'cure' and their assessment of outcome following treatment of lower urinary tract dysfunction.

Objectives

Primary objective

The primary objective of this study was to determine what clinicians perceive as 'cure' and to evaluate which urinary symptoms are felt to be troublesome, and which are acceptable, following treatment.

Secondary objective

The secondary objectives were to assess the method of outcome assessment used both in the everyday clinical setting, and the research environment, following the treatment of lower urinary tract dysfunction.

Patients and Methods

Study Population

Clinicians were recruited from the membership list of the United Kingdom branch of the International Continence Society (ICS UK). All of those identified from the mailing list professed to have a specialist interest in lower urinary tract dysfunction in women; the membership including urogynaecologists, urologists, obstetricians and gynaecologists in addition to continence advisors, specialist nurses and physiotherapists.

Inclusion Criteria

All consenting English-speaking clinicians, caring for women with lower urinary tract dysfunction, who completed the questionnaire, were eligible for inclusion in the study.

Exclusion Criteria

Clinicians were excluded from the study if they met one of the following exclusion criteria:

Questionnaire not returned and/or Questionnaire not completed satisfactorily.

Methods

All members that were identified from the ICS UK mailing list were sent a structured questionnaire in addition to a covering letter detailing the purpose of the study and a reply paid envelope. The questionnaire itself was divided into five sections;

The first asked which lower urinary tract symptoms would be acceptable following treatment. Three responses for each symptom were available (yes / probably / no).

The second asked what they felt would be a good (but realistic) outcome following treatment

The third asked what outcome assessment was routinely used in clinical practice.

The fourth asked what method of outcome assessment was used in the research setting.

The final question simply asked which urinary symptom was considered to be most troublesome.

In general the questionnaire took around five minutes to complete. All responses received within 12 weeks of the questionnaire mailing date were included in the data analysis. No follow up letters or reminders were sent.

Statistical Methods

Questionnaire results and urodynamic diagnosis were recorded and a database compiled. The database was then checked for accuracy and analysed using the Statistical Package for Social Sciences (SPSS, version 10 for Windows). Findings were simply expressed as a proportion of the total population for each field studied.

Table 6. — Occupation of Respondents.

Occupation	Number (%)
Urogynaecologist	33 (21.3)
Urologist	29 (18.6)
Gynaecologist	21 (13.5)
Obstetrician and Gynaecologist	20 (12.8)
Physiotherapist	21 (13.5)
Continence Nurse	17 (10.9)
Continence Advisor	5 (3.2)
Geriatrician	3 (1.9)
Physician	1 (0.6)
Clinical Scientist	1 (0.6)

Results

In total 299 questionnaires were distributed and 156 were returned completed correctly, giving a response rate of 52.7%. The occupation of respondents is shown in Table 6.

Overall expectations following treatment

Overall 85.9% of responding clinicians felt a good improvement in urinary symptoms, so that they no longer interfered with quality of life, was a realistic outcome whilst just 3.2% hoped for a complete cure (Table 7).

Unsurprisingly only one clinician hoped for “any improvement, no matter how small”.

Sub-group analysis by profession did not show any differences in expectations regarding outcome or acceptability of symptoms following treatment.

Acceptability of symptoms following treatment

In general the majority of clinicians thought that small or infrequent episodes of leakage were acceptable following treatment although frequent or large leaks were not. Irritative urinary symptoms such as urgency and urge incontinence were felt to be less acceptable as were the symptoms of frequency and nocturia. The majority of clinicians considered having to use pads on an occasional basis was reasonable although constant use of incontinence pads was not. In addition leakage during intercourse was felt to be unacceptable (Table 8).

Table 7. — Overall Expectations Regarding Treatment.

Complete cure of all bladder symptoms	5 (3.2%)
A good improvement so they no longer interfere with your life	134 (85.9%)
Being able to cope better so your life is affected less	16 (10.2%)
Any improvement in your bladder symptoms, no matter how small	1 (0.6%)

Table 8. — Acceptability of symptoms following treatment.

	Yes	Probably	No
Never ever leaking no matter what you do	90%	3%	6%
Occasional small leak on coughing or sneezing	49%	35%	14%
Occasional small leak on strenuous exercise	54%	37%	8%
Occasional large leak on coughing or sneezing	3%	19%	76%
Frequent small leaks on coughing or sneezing	0%	8%	91%
A sudden urge or need to pass water (no leaking)	19%	45%	34%
Occasionally leaking before reaching the toilet	7%	40%	51%
Having to pass water very often during the day	3%	19%	76%
Having to get up once at night to pass water	72%	22%	6%
Having to get up twice or more at night to pass water	6%	28%	63%
Occasionally having to wear panty liners ‘just in case’	41%	47%	12%
Occasionally having to wear pads ‘just in case’	18%	42%	39%
Having to continue to wear pads most of the time	1%	5%	92%
Leaking during sexual intercourse	4%	19%	77%

Most troublesome lower urinary tract symptoms

Clinicians were also asked to comment on which lower urinary tract symptoms they considered to be most bothersome. Despite this being a ‘free text’ item on the questionnaire several themes were seen to develop. The most commonly reported bothersome symptoms were urinary incontinence (12.3%), urge incontinence (10.7%), urgency and frequency (4.6%) and nocturia (2.6%). Other responses to this question included bladder pain, embarrassment and fear.

Assessment of Outcome

In general outcome assessment was more rigorous in research when compared to clinical practice. In the research setting 61% felt both subjective and objective measures should be used as assessment of treatment whilst in clinical practice 42% thought subjective improvement alone, and 36% subjective improvement in QoL, were appropriate. Few clinicians were routinely using pad testing alone and few used objective measures in clinically (Table 9).

Discussion

At present there is no consensus of opinion regarding the definition of cure amongst patients (Robinson *et al.*, 2004) or between clinicians (Hilton, 2002). Overall our findings have shown that most clinicians are realistic in their expectations following treatment with 85.9% of clinicians hoping for a good improvement so that there was less of an effect on quality of life. In addition, only 3.2% would expect a complete cure of all urinary symptoms, acknowledging the limitations of both medical and surgical therapy, whilst only 0.6% hoped for any improvement ‘no matter how small’. This perhaps reflects the fact that all those surveyed had a particular interest in lower urinary tract dysfunction.

Interestingly, when considering the views of patients, again the majority of respondents hoped for a good improvement although this only amounted to 43%. Patients tended to be both more optimistic, with almost a fifth hoping for a complete cure of all symptoms, and almost equally pessimistic, with 10% hoping for any improvement what so ever. These findings may represent patient perceptions of ‘cure’

Table 9. — Assessment of Outcome.

	Research	Clinical
Subjective improvement in symptoms	7.7%	42.6%
Subjective improvement in QoL	8.3%	36.1%
Objective cure on urodynamic testing	1.9%	0.6%
Objective cure on pad testing	3.2%	1.3%
Subjective (QoL) and objective (urodynamic) cure	17.9%	4.5%
Subjective (QoL) and objective (pad test) cure	30.1%	11.6%
Subjective (QoL) and objective (urodynamic/ pad test) cure	30.8%	3.2%

following previous medical and media exposure. An interesting extrapolation of these findings is that there is a group of patients who, from a clinical viewpoint, are considered a treatment failure but may actually be content with the residual symptoms which they have.

The difference in expectations regarding outcome of treatment has also been assessed in a large prospective questionnaire based cohort study of 442 women undergoing incontinence surgery in 49 centres in the North Thames region of South East England (Black *et al.*, 1997). Overall 87% of women reported an improvement in severity of stress incontinence and 71% an improvement in mental health. One year following surgery 72% continued to feel better and 66% felt that the treatment had exceeded their expectations. 68% would recommend the operation to a friend. Interestingly surgeons tended to be more optimistic; they were satisfied with the outcome in 85% of cases and would again treat 94% of women as they had done previously. Whilst this study is based on subjective measures only it again highlights the fact that the concept of 'cure' differs regarding the outcome measures used and populations sampled.

Acceptability of Symptoms

When considering the acceptability of symptoms following treatment there were considerable differences between the views of patients and clinicians. The majority of clinicians thought small episodes of stress leakage were generally acceptable although this was not the case in patients, with less than a third considering this to be acceptable. Those irritative symptoms of urgency and urge incontinence were felt to be unacceptable to the majority of both clinicians and patients, and this would certainly be in keeping with previously studies showing a greater impact on QoL in those patients with detrusor overactivity. Interestingly frequency was felt to be more unacceptable by clinicians (76%) than patients (34%) and this may reflect the effect of studies of antimuscarinic agents where reduction in diurnal frequency is often the primary outcome measure used. Whilst having to rise once at night to void was universally felt to be acceptable nocturia, rising two or more times at night, was felt to be much more troublesome in both groups. Again, these findings would support previous QoL studies showing a marked deterioration in patients complaining of nocturia. Furthermore almost identical numbers in both groups would find leakage during intercourse to be unacceptable.

When considering containment strategies more clinicians than patients thought it was acceptable to

wear a panty liner 'just in case' (41% vs 20%) although both groups were more reluctant to consider the use of pads. Unsurprisingly clinicians would not find the constant wearing of pads acceptable although almost 10% of patients would. These findings would support those looking at expectations of outcome where again patients tended to be more pessimistic than clinicians.

Assessment of Outcome

At present there is no consensus of opinion regarding methods of outcome assessment either in a clinical or research setting. Whilst subjective assessment is most often used clinically by simply asking patients about symptoms or satisfaction regarding outcome objective measurements are used more often in clinical trials and research. The purpose of this part of the study was to determine which outcome measures were being used throughout the United Kingdom both clinically, and in research projects.

Our results have shown that, as may be expected, resolution of clinical symptoms are used most frequently as an outcome measure in the clinical setting (42.6%) although a third (36.1%) did use QoL measures. Fewer clinicians would consider the use of objective tests of outcome following treatment; the most commonly cited investigation being a pad test (11.6%). The practice in our own unit here at King's is to reassess patients with subjective QoL measures and objective tests such as urodynamic studies. In the clinical setting only 4.5% of clinicians performed similar outcome assessment with slightly fewer combining this with a pad test.

Unsurprisingly, when looking at outcome measures used in the research setting clinicians tended to be more exacting in their assessments with only 7.7% relying on subjective measures alone and the majority, over 60%, using a combination of both subjective and objective outcome measures. Clearly, when assessing new surgical or medical treatments, it is imperative to accurately evaluate outcome objectively. However, at present many surgical trials are published with subjective short-term evaluations only and lack objective efficacy data. Equally, the majority of pharmaceutical trials lack evidence of objective change in urodynamic parameters although the use of bladder diaries, urgency scales and frequency/volume charts does provide some objective evidence of treatment effect in addition to the subjective assessments using QoL measures. This would seem to represent a paradox in terms of the expectations of clinicians and reality of clinical trial reporting.

The importance of treatment outcomes amongst patients, nurses and medical staff has recently been

reported. Visual analogue scales were used to evaluate the relative importance of five clinical outcomes. Subjective improvement and improvement in QoL were rated most highly and the authors conclude that these should become primary outcome measures in future clinical trials (Tincello and Alfirevic, 2002).

Definition of cure and outcome measures may also have a significant effect on the outcome of clinical studies. In the UK multicentre randomised comparative trial of Burch colposuspension and tension free vaginal tape (TVT) cure rates were found to vary depending on the outcome parameters reported (Ward and Hilton, 2002). Cure rates based on objective testing varied between 80% and 65% with subjective cure rates between 60% and 30%. Despite overall patient satisfaction rates being 70% and 83% for colposuspension and TVT respectively combined objective and subjective cure rates fell to 26% for both procedures. From this it is evident that success rates are dependent on the definition of cure used although there remains no consensus of opinion as to which is most appropriate.

Study Design and Appraisal

In order to gain an insight into the views and opinions of clinicians treating women with lower urinary tract dysfunction we approached the International Continence Society (UK) who provided a list of members. This allowed the inclusion of a broad spectrum of specialists including doctors, nurses and physiotherapists, thus providing a cross section of opinions and attitudes.

A limitation of all postal questionnaire studies, including this one, is the number of questionnaires returned and thus the response rate. In order to maximise this we provided a covering letter explaining the purpose of the study as well as a reply paid envelope. The overall response rate of 52.7% is in keeping with those of other questionnaire based studies. By performing a further mailing, four weeks after the first, we may have been able to increase this further although this was not done due to constraints of time and cost.

A further possible confounding factor with questionnaire-based research is one of confidentiality. In order to gain an accurate view of clinician's opinions we thus blinded the responses so no particular unit or clinician could be identified.

Conclusions

This study has provided an insight into the clinician's concept of cure and also how cure, or outcome is assessed both in a clinical and research setting. By comparing the views of the clinician to that of the

patients we have also been able to demonstrate the differences and similarities between these two groups with regard to bothersomeness of symptoms and overall expectations of treatment. These findings may help to explain why patients may be disappointed regarding treatment outcomes and why there may be a difference between subjective clinical impression of success and patient satisfaction.

3. Anti-diuresis in the Management of Daytime Urinary Incontinence

Rationale

In women who complain of urge incontinence or mixed incontinence behavioural therapy and drug treatment are considered the most effective whilst those who complain of stress incontinence may benefit from physiotherapy or incontinence surgery. Neither is without risk or unwanted effects. Antimuscarinic medication is associated with typical anticholinergic side-effects such as dry mouth, constipation and blurred vision whereas surgery, in addition to inherent intra-operative risks, may lead to voiding dysfunction and 'de novo' detrusor overactivity. Compliance with medical therapy is also a significant problem. In a questionnaire follow-up study of women with detrusor overactivity just 5.5% were cured of their urinary symptoms and only 18.2% of women continued drug therapy for more than six months.

Desmopressin (Minirin, 1-desamino-8-D-arginine vasopressin (DDAVP)) is a synthetic nonapeptide analogue of anti-diuretic hormone (ADH). It has a potent anti-diuretic action of rapid onset leading to decreased urine production and a corresponding increase in the time taken to reach bladder capacity. Currently desmopressin is used in the management of diabetes insipidus, nocturnal enuresis and nocturia in patients with multiple sclerosis" although it does not have a license for the management of nocturia in the non – neuropathic patient as yet.

The purpose of this study was to determine whether the anti-diuretic properties of desmopressin could be used as a 'designer' treatment in women with daytime urinary incontinence allowing them to choose when they require treatment.

Null Hypothesis

This study was designed to test the hypothesis that desmopressin had no effect on daytime episodes of urinary incontinence and that there would be no difference between the active and the placebo treatment arms of the study.

Objectives

Primary objective

The primary objective of the study was to investigate the efficacy of desmopressin treatment on urinary incontinence during the first four hours following drug administration.

The primary efficacy parameter was the number of periods with total dryness for four hours following drug administration.

Secondary objectives

The secondary objectives of the study were to investigate the voiding pattern up to 24 hours following dosing and to assess safety in the patient population.

The secondary efficacy and safety parameters were:

The volume voided per episode

Total volume voided

Time to first void or incontinence episode

Number of periods with total dryness

Number and type of adverse events

Patients and Methods

Study Design

This was an exploratory double-blind, randomised, placebo-controlled cross-over study that was designed to investigate the concept of anti-diuresis in the management of women with daytime urinary incontinence (stress, urge or mixed).

It was considered necessary to include a placebo treatment to adequately assess the potential clinical usefulness of desmopressin in patients with urinary incontinence. The study was double-blind and randomised in order to limit any patient or investigator bias. A cross-over design was selected so that each patient was her own control and to decrease the variation between patients and thus increase the power to detect a difference between desmopressin and placebo.

The study was performed in three centres in the United Kingdom and Europe: Kings College Hospital (London, UK), Borås County Hospital (Boras, Sweden) and Skejby Hospital (Aarhus, Denmark).

Study Population

Women were recruited from tertiary referral urogynaecology clinics in each of the three study centres. All had been referred with troublesome lower

urinary tract symptoms and complained of severe daytime urinary incontinence. Information regarding the study was provided verbally in addition to a written information sheet. Written informed consent was obtained prior to inclusion.

Inclusion Criteria

The following inclusion criteria were used; Women aged 18 years to 80 years complaining of severe stress, urge or mixed incontinence.

Informed written consent

Exclusion Criteria

Patients were excluded from the study if they met one of the following exclusion criteria:

Current use of anti-muscarinic therapy for urge or mixed incontinence.

Current conservative measures such as pelvic floor exercises or bladder retraining.

Active lower urinary tract infection.

Low serum sodium at trial entry (below 135 mmol/l).

Fluid intake exceeding 2.5 litres during the run in period of the trial.

Concomitant treatment with drugs known to interact with desmopressin such as: diuretics, tricyclic anti-depressants, indomethacin, carbamazepine and chlorpropamide.

Pregnant or lactating women and sexually active women of child bearing age who were not using a proven, reliable method of contraception.

A history suggestive of neurogenic detrusor overactivity.

A history of alcohol dependency, recreational drug usage or psychiatric disorder.

Trial Medication

Desmopressin (Minirin®, Ferring Pharmaceuticals) nasal spray and matching placebo were supplied by Ferring Pharmaceuticals (Copenhagen, Denmark) who were also the sponsors of the study. Drugs were self administered by the women throughout the study using the intranasal route. The dosage used was 40mcg (two puffs in each nostril) or matching placebo and the treatment regimen consisted of 10 single administrations (seven desmopressin and three placebo) over the four-week duration of the trial. In order to have the best chance of demonstrating an effect in urinary incontinence, a relatively high dose of 40 mg was chosen. In addition the nasal formulation was selected since bioavailability is 20-40 times higher than that of the oral route of delivery.

Women were given both verbal and written instructions on drug administration. Before dosing women were asked to prime the spray by pumping the nozzle ten times into the air. They were then asked to administer one puff to each nostril, wait for a minute, and then administer a further one puff to each nostril, the total dose of desmopressin being 40mg. Women were asked to take the study medication at least four hours before bedtime and to try and avoid taking the drug on consecutive days since a washout period of 24 hours was required. There were no specific instructions given regarding dosing with respect to meals and patients were asked to refrain from using the trial medication during menstruation as this would make assessment more difficult.

Blinding

The study treatments were packaged for individual patients according to a computer generated randomisation code. The appearance and labelling of the active medication and the placebo were the same. This randomisation code was not available to the patient or site investigators although emergency decoding envelopes containing the treatment sequences were available and were kept in pharmacy.

Randomisation and Treatment Allocation

A computer generated randomisation scheme was prepared by Ferring Pharmaceuticals. Patients were randomised to one of four treatment sequences in blocks of eight. The study centre was identified by the first digit in the patient number and patient numbers were allocated sequentially in the order in which the patients were enrolled.

The placebo days were randomised in the ten days of treatment using four sequences. These four sequences were selected taking into account that for each treatment day both treatments should be present.

Statistical Methodology and Analysis

Power Calculation

This study was exploratory in nature and therefore no formal power calculation was performed.

Analysis Populations

Three analysis populations are defined in the study.

1) The Intention to Treat (ITT) population includes all randomised patients having received at least one dose of study medication and thus having treatment efficacy data.

2) The Per-Protocol Population (PP) includes all patients who received 10 days of study treatment, had no major protocol violations and had no more than two consecutive days with missing endpoint data (to ensure that at least one day of placebo is concluded).

3) The Safety Population (SP) includes all patients exposed to study medication.

When considering analysis of the study results the primary objective was assessed for the ITT and PP populations whilst the secondary objectives were assessed for the intention to treat population. Finally, the study safety analysis was based on the SP.

Statistical Analysis

The null hypothesis was that there would be no difference between the active and the placebo treatments. All statistical analyses were performed as two sided at a 5% significance level and no co-variate adjustments were performed for demographic or baseline characteristics.

Primary Endpoint

The primary efficacy endpoint (number of periods without leakage for the first four hours post dose) was transformed into incidences and analysed using the two-sided paired Student's t-test. The incidence for each subject during each treatment was calculated as the number of periods without leakage divided by the number of recordings. This analysis was performed for the ITT and PP populations. In addition odds ratios were calculated using the Cochran – Mantel Haenszel test.

Secondary Endpoints

The analysis of the secondary endpoints was performed using descriptive statistics including calculation of the means, standard deviation, medians, ranges and confidence intervals for both treatment arms. This analysis was performed for the ITT population only.

Methods

Prior to trial entry all women underwent a full clinical history and physical examination. Urinalysis was performed to exclude a lower urinary tract infection in addition to a venous blood sample to estimate serum sodium and creatinine and a urine pregnancy test. Those women taking diuretics, tricyclic anti-depressants, indomethacin, carbamazepine and chlorpropamide, or who had an

abnormally low serum sodium were excluded from entry into the study.

Following the initial visit women were provided with a urinary diary and asked to record fluid intake, voids and episodes of urinary leakage over a five-day period (including a weekend). In addition they were instructed to weigh themselves morning and evening. Subsequently on review of the diary at the second visit, if the entry criteria were met, and the daily fluid intake was not in excess of 2.5 litres they were randomised to receive one of four treatment sequences. Each sequence consisted of seven single doses of desmopressin (Minirin, Ferring Pharmaceuticals) nasal spray 40 mg and three single doses of identical placebo which were taken consecutively.

Women were instructed to take the medication at a time of their own choosing although not less than four hours before bedtime, not on more than two consecutive days and not more than once in 24 hours. They were again provided with a urinary diary and asked to record voids and episodes of urinary leakage. As an additional safety parameter they were asked to weigh themselves at the time of drug administration and exactly 24 hours later. If the weight gain was in excess of 2% of total bodyweight they were asked to contact the hospital so a serum sodium level could be checked. In order to objectively measure urinary leakage all women were provided with a supply of incontinence pads (Tena®, SCA Hygiene Products, Sweden) which they were asked to change at 4, 8, 12 and 24 hours following drug administration (with the exception of 8 and 12 hours if the patient was asleep). Women were asked to weigh their pads immediately before use and again on removal. An increase in pad weight of more than 5 g was considered significant and for the determination of volume leaked per episode it was assumed that 1 g was equivalent to 1 ml.

Results

Seventy-five women were screened of which 64 were included and randomised into the study. Forty-

one patients were recruited in the UK, 17 in Sweden and 6 in Denmark. There were 11 screening failures; consent withdrawn (4), incontinence not confirmed during the screening period (4), positive pregnancy test (1), taking prohibited medication (1) and fluid consumption of > 2.5 litres a day (1). Sixty women were exposed to study medication. Of the 64 randomised patients 57 completed the study. A total of 7 (11%) patients withdrew including 2 (3%) for adverse events and 5 (8%) patients did not return for their final follow-up visit.

The mean age at trial entry was 53.3 years (range 24.9-78.0), mean body weight 74.7 kg (range 43.7-123.0) and mean height 161.6 cm (range 150-182). All women complained of severe daytime urinary incontinence; 15 women had predominantly stress incontinence, 13 predominantly urge incontinence and 32 mixed incontinence.

During the five day screening period the mean 24-hour urine output was 1557 mls (range 180-2868), and mean number of incontinence episodes were 2.7/24 hrs (range 1.0-9.2). The mean volume leaked per incontinence episode was 28.3 mls (range 9.0-96.0). Mean fluid intake during the screening period was 1416 mls, none of the women drinking more than 2500 mls.

The primary efficacy endpoint was the number of periods without leakage (defined as ≤ 5 g pad weight increase) for the first four hours post voiding. There was a significantly ($p < 0.001$) higher incidence of periods without leakage of 61.7% four hours following desmopressin administration compared to 47.9% on placebo in the ITT population (Table 10).

In the PP protocol the results were similar, $68.4 \pm 33.6\%$ vs $54.5 \pm 39.3\%$ ($p = 0.002$). The odds of having an episode without urinary leakage during the first four hours was 172% higher on desmopressin than on placebo (odds ratio = 2.72, 95% CI: 1.6-4.8, $p < 0.001$). These results were identical in the PP population. In addition there was a higher frequency of periods without leakage on desmopressin when compared to placebo; 36% of women in the desmo-

Table 10. — Incidence of periods without leakage in the first 4 hours.

Incidence (%)	Desmopressin	Placebo	Difference
Number	58	55	54
Mean (SD)	61.7 (35.4)	47.9 (40.2)	14.4 (28.1) ^b
Median	71.4	50.0	9.5
Min - Max	0.0 – 100.0	0.0 – 100.0	-42.9 – 85.7
Confidence Interval ^a	52.4 – 71.0	37.0 – 58.7	6.7 – 22.1

a. Two sided 95%

b. $p < 0.001$. Two sided pared students t test.

Table 11. — Secondary endpoint variables in the first 4 hours.

Volume Leaked Per Incontinence Episode (ml)	Desmopressin	Placebo	Difference
Number	45	39	36
Mean (SD)	22.2 (18.9)	26.1 (25.1)	-1.4 (20.4)
Median	15.0	15.0	0.0
Min – Max	6.0 – 97.5	9.0 – 105.0	-65.8 – 72.5
Confidence Interval ^a	16.5 – 27.9	17.9 – 34.2	8.3 – 5.5
Total Volume Voided (ml)	Desmopressin	Placebo	Difference
Number	59	58	58
Mean (SD)	237 (121)	317 (194)	-82 (180)
Median	212	258	-57
Min – Max	74.3 – 642.9	92.5 – 1090	-810 – 318.0
Confidence Interval ^a	205.7 – 268.7	266.1 – 368.3	-129.2 – -34.6

a. Two sided 95%.

pressin group had no leakage on virtually all (6 or 7) treatment days for four hours following administration. Again the results for the PP population were similar. There were no differences in outcome when analysed according to type of incontinence or recruitment centre. In addition the total volume voided (237 mls) in those women taking desmopressin was lower than on placebo (317 mls) over the first four hours (Table 11).

During the time period of 4-8 hours following drug administration there was a smaller, although not significant, difference between treatments, with a $67.8 \pm 35.4\%$ incidence of periods without leakage on desmopressin versus $62.7 \pm 40.8\%$ on placebo. Furthermore there were similar differences when comparing total volume voided and volume leaked per incontinence episode. There was no difference between desmopressin and placebo for the incidence of periods without leakage during the time period of 8-12 hours following drug administration. Mean total voided volume however was slightly lower on desmopressin (230 ± 121 mls) when compared to placebo (310 ± 192 mls).

When considering the time period of 0-8 hours following administration there was also a higher incidence of periods without leakage of $54.7 \pm 36.5\%$ on desmopressin versus $40.1 \pm 41.0\%$ on placebo. This was similar to that observed during the first four hours. In addition the total volume voided and volume leaked per incontinence episode was slightly lower on desmopressin.

At 12-24 hours following drug administration there were no apparent differences between desmopressin and placebo for periods without leakage and volume leaked per incontinence episode. However, mean total volume voided was again lower in the desmopressin group.

Overall during the time period of 0-24 hours post dosing there was a higher incidence of periods without leakage of 32.7% on desmopressin compared to 25.3% on placebo (Table 12). However, both the absolute incidence of periods without leakage and the difference between desmopressin and placebo were less than that observed in the first four hours. There was an overall lower mean 24-hour total voided volume of 1180 mls on desmopressin versus 1375 mls on placebo. Volume leaked per incontinence episode was slightly lower on desmopressin compared to placebo (Table 12).

Finally, the time from drug administration to first episode of incontinence (defined as difference in pad weight ≥ 5 g) or void was slightly longer on desmopressin (2.3 ± 1.0 hrs) compared to placebo (2.1 ± 1.0 hrs). In addition time to first incontinence episode was longer on desmopressin (6.3 ± 2.5 hrs) compared to placebo (5.2 ± 3.3 hrs).

Regarding safety 35 women (58%) reported a total of 142 adverse events during the study period as a whole. Of these 25 (42%) patients reported a total of 87 adverse drug reactions (assessed as possible/probable related to drug) on desmopressin whilst 15 (25%) reported 24 adverse drug reactions on placebo. There were no serious or life-threatening adverse events and those most commonly reported on desmopressin were headache (36%) and nausea (10%). Specifically there were no episodes of significant weight gain following drug administration and no cases of hyponatraemia detected. Two patients withdrew; one had an allergic reaction to desmopressin whilst the other complained of malaise, fatigue and abdominal discomfort. Overall no events were described as severe, and 80% of adverse events on desmopressin, and 90% on placebo, were described as mild in intensity.

Table 12. — Secondary endpoint variables over 24 hours.

Incidence of periods without leakage (%)	Desmopressin	Placebo	Difference
Number	57	50	50
Mean (SD)	32.7 (38.1)	25.3 (37.7)	9.5 – 34.3
Median	16.7	0.0	0.0
Min – Max	0.0 – 100.0	0.0 – 100.0	-71.4 – 100.0
Confidence Interval ^a	22.6 – 42.9	14.6 – 36.0	-0.2 – 19.2
Volume leaked per Incontinence episode (ml)	Desmopressin	Placebo	Difference
Number	51	48	46
Mean (SD)	24.3 (18.6)	25.7 (18.5)	-2.1 (15.2)
Median	16.4	17.6	-1.4
Min – Max	6.0 – 95.0	8.5 – 82.2	-31.0 – 70.0
Confidence Interval ^a	19.1 – 29.6	20.3 – 31.1	-6.6 – 2.4
Total Volume Voided (ml)	Desmopressin	Placebo	Difference
Number	58	57	56
Mean (SD)	1180 (582)	1375 (625)	-246 (504)
Median	1041	1300	-167
Min – Max	290.7 – 2986	300.0 – 3450	-2161 – 1200
Confidence Interval ^a	1026.7 – 1332.7	1209.4 – 1541.2	-380.8 – -110.8

a. Two sided 95%.

Discussion

This is the first study to explore the concept of anti-diuresis as a management strategy for daytime urinary symptoms in women and, whilst a proof of concept study, would suggest that desmopressin offers safe and effective treatment for women with urinary incontinence. The study had a pragmatic design allowing women to choose when they wished to take treatment with regard to their daily activities. The ability to decide when to take medication may improve motivation and compliance and this is reflected in the low withdrawal rate from the study despite comprehensive diaries. These findings are significantly better than previously reported compliance rates whilst taking anticholinergic therapy.

Desmopressin has a potent anti-diuretic effect, being used in the management of diabetes insipidus and nocturnal enuresis. More recently it has been evaluated in the management of nocturia in both neuropathic (Hilton *et al.*, 1983; Valiquette *et al.*, 1996) and non-neuropathic patients (Mattiasson *et al.*, 2002). The rationale for using desmopressin in daytime urinary incontinence was that by decreasing urine production there would be a prolonged bladder filling time and hence an increase in the time taken to reach functional bladder capacity. At present desmopressin does not have a licence for the management of urinary incontinence.

Primary and Secondary Outcome Variables

The results of this study show that desmopressin is effective in the treatment of daytime urinary incontinence. When considering the primary endpoint there was a higher incidence of periods without leakage in the first four hours following drug administration when compared to placebo (61.7% Vs 47.9%). In addition there was a higher frequency of dry days on desmopressin than placebo and 36% of patients had no leakage on virtually all of the treatment days. For four hours following drug treatment. Overall, during the first 8 hours after drug administration there was a higher incidence of periods without leakage on desmopressin when compared to placebo (54.7% Vs 40.1%).

Study Design and Appraisal

Desmopressin may be administered via the oral or intranasal route. Whilst bioavailability is very low with oral administration (< 1%) this is slightly improved with intra-nasal use (2%-10%). The intranasal route of administration has previously been shown to be effective in the management of urinary symptoms and consequently was chosen as the preferred method of drug administration in this study. Since this was a feasibility study a relatively high dosage was used (40 mg) and this also ensured that

all patients received a high enough dosage to induce an anti-diuretic effect without having to measure drug plasma levels following administration.

The study was double blind to avoid bias whilst a cross over design was used so that each patient would act as her own control. During the course of the study each subject took seven doses of desmopressin and three doses of placebo. Consequently it could be argued that quantitative differences between treatments are biased due to the unbalanced design of the trial. However, similar differences between treatments during the first four hours were obtained using a more balanced approach with a limited data set of the first 3 days on desmopressin and 3 days on placebo. This further supports that desmopressin is effective and excludes the possibility of bias.

As previously reported studies have shown there is a considerable placebo response rate in trials assessing the management of women with lower urinary tract symptoms (Meyhoff *et al.*, 1983). This is supported by the findings of this study where the placebo response was 47.9%. Participation in clinical studies involves a high degree of interaction between subjects and investigators and this, in conjunction with advice regarding fluid intake and diet, all acts as a form of bladder retraining. In addition the completion of urinary diaries serves as a form of biofeedback hence compounding the effect. This is a confounding feature of all clinical studies involving the management of urinary incontinence and is not unique to this study.

Safety Analysis

Whilst overall the drug was found to be safe and well tolerated there was an increased incidence of adverse events on desmopressin when compared to placebo. However this too may partly be explained by the design of the study since desmopressin was taken for seven days (70% of study duration) and placebo for only three (30%). Whilst there is a documented risk of water retention and hyponatraemia using desmopressin therapy (Robson *et al.*, 1996) (Schwab and Ruder, 1997) there were no reported problems in this study. In this study safety parameters included serum sodium and creatinine at trial entry as well as serial body weight assessment and advice regarding fluid intake fluid. In the clinical situation care should be taken in the elderly and a serum sodium checked shortly after commencing medication.

However, whilst there were no safety concerns in this study, it should be noted that due to recent reported problems with hyponatremia the indication for the nasal formulation of DDAVP has recently been withdrawn in many countries worldwide.

Conclusions

In summary the results of this exploratory study would suggest that desmopressin is a safe and effective treatment in women complaining of daytime urinary incontinence. Although not suitable for everyday usage it allows women to choose when they require treatment and this may improve acceptability and compliance.

Statistical significance may not always be the same as clinical significance which is useful in everyday practice. Although the incidence of periods without leakage only reached statistical significance in the first four hours following drug administration the findings would suggest that the clinical benefit and corresponding improvement in lower urinary tract symptoms is significant up to 24 hours following administration and therefore offers benefit in clinical practice.

Desmopressin, by acting as an anti-diuretic, also avoids the troublesome side effects of dry mouth, constipation and somnolence associated with antimuscarinic medication, hence providing a rationale for women who are unable to tolerate side effects associated with more conventional treatment. Since desmopressin was equally efficacious in women with stress, urge and mixed incontinence it may also prove useful in those women who are waiting for surgery or whose symptoms are only intermittent in frequency or severity.

This exploratory study suggests that the concept of using an anti-diuretic agent should be further explored in a larger confirmatory randomised trial.

4. Final Conclusions and Future Research

Urinary incontinence and lower urinary tract dysfunction, whilst not life threatening, remain an important cause of morbidity in women and the effect on quality of life has been extensively documented (Kelleher *et al.*, 1997). The management of women with urinary incontinence is dependent on the mechanism of the underlying pathology; those with a diagnosis of urodynamic stress incontinence who fail conservative measures may be offered continence surgery whilst those with detrusor overactivity or overactive bladder syndrome are usually managed using a combination of bladder retraining and drug therapy.

The use of anti-muscarinic agents remains central in the management of women complaining of urge incontinence although they are known to be associated with troublesome side effects, hence affecting patient compliance. The development of newer longer acting drugs and drugs with greater bladder

selectivity has helped improve patient acceptability to some extent although many women still do want to take regular medication with frequent adverse effects. Equally those women with symptoms of stress incontinence may not contemplate the possibility of surgery because of the associated risks and complications.

This may be because they do not perceive their urinary problems to be severe enough to warrant long-term therapy or alternatively it may be because their symptoms are only troublesome in certain situations. Consequently the availability of a safe, efficacious and easily administered medication which can be used as required may lead to an improvement in patient acceptability, compliance and ultimately satisfaction.

The papers presented in this thesis have introduced the concept of interpretation of the patients' and clinicians' concepts of what constitutes an effective and acceptable treatment and what is regarded as a successful outcome. The evidence would suggest that there is an unmet patient need for a 'designer drug' for daytime urinary incontinence to be used as and when required. The use of a novel approach using an anti-diuretic agent may provide a useful alternative to the use of standard treatment algorithms in both stress and urge incontinence.

Lower Urinary Tract Dysfunction: Patient expectations

Until relatively recently there has been a paucity of data regarding patient expectations following treatment for lower urinary tract function. Expectations regarding outcome are shaped by previous personal experiences, those of friends and relatives and also by the attitude and experience of the clinician. Consequently the concept of 'cure' is relative. Achieving continence may not be regarded as a cure if new symptoms of urgency, frequency and recurrent infections are experienced following surgery or a dry mouth and constipation during drug therapy.

Quality of life (QoL) has often been used as a surrogate measure of patient satisfaction and success following treatment and many disease specific questionnaires have been developed for use in women complaining of lower urinary tract symptoms. Improvement in QoL is seen as a powerful indicator of effective treatment although at present there is little evidence to clarify what constitutes a significant or meaningful change. To address this the Kings Health Questionnaire (KHQ) has recently been re-evaluated to assess the minimal important difference which is clinically meaningful (Kelleher *et al.*, 2004). Using an anchor and population based approach it was found that a change from baseline of at least five

points indicates a change that is meaningful to patients and is indicative of a clinically meaningful improvement. This provides a further outcome measure by which 'cure' may be assessed.

In the papers presented in this thesis we asked patients what they perceived as a cure and also, following treatment, which symptoms they would be happy to tolerate and which they would not. An alternative way of looking at patient expectations of treatment is that of patient orientated goals and this has recently been investigated in 36 women undergoing surgery for pelvic floor dysfunction (Hullfish *et al.*, 2002). Pre-operatively each patient identified five personal goals that they hoped to achieve following surgery and were then asked to report whether these had been met at follow up. Of those identified 42.9% dealt with urinary or bowel symptoms, 30.3% with improving activity, 12.6% with general health, 11.8% with social relationships and self image and 2.5% with physical appearance. At 6-week follow up women agreed that most goals had been met for activity, symptoms, general health and appearance although not for self-image. However, by 12 weeks goals were met in all categories. More recently longterm follow up has been reported revealing that the self reported achievement of goals persisted for one to three years following surgery and that goal achievement is related to more general QoL measures (Hullfish *et al.*, 2004).

Assessing patient expectations of treatments, both medical and surgical, may allow a more accurate measure of success or cure and, whilst difficult to objectively measure or quantify, may allow individual management strategies to be tailored to particular patient requirements. Setting jointly agreed goals or aims prior to commencing a course of treatment may improve patient satisfaction and also act as a measure of 'cure'.

At present there have been no studies reported regarding the expectations of medical treatment for lower urinary tract and pelvic floor dysfunction and work investigating this is currently under development in our department in addition to comparing goals of treatment with QoL based outcomes. Equally it would be interesting to investigate how treatment, either medical or surgical, affects patients interpretation of cure and whether this changes over time.

Patient expectations regarding their treatment and the development of a patient and physicians 'contract' to establish treatment goals prior to surgery or medical therapy, may lead to greater patient satisfaction and provide a more meaningful measure of outcome and consequently offer a definition for 'cure'.

Lower Urinary Tract Dysfunction: Clinical expectations

The concept and understanding of 'cure' also may also have different implications between clinicians as well as between clinicians and patients. What a physician regards as a successful outcome may not always agree with the patients' perception leading to dissatisfaction and a ultimately a loss of trust. This may be caused by unrealistic expectations, an unsuccessful outcome or the development of complications. This dichotomy of opinion regarding outcome has been illustrated by questionnaire-based study of patients before and after continence surgery performed in the North Thames area of London (Black *et al.*, 1997). Overall 87% of women were satisfied with the outcome and 68% would recommend the operation to a friend although only 28% were continent. Whilst this again illustrates the problems of defining 'cure' the authors also found that surgeons tended to be more optimistic with satisfaction rates of 85% and 94% would again treat women as they had done previously.

At present there is no generally accepted standard that is accepted amongst clinicians as to which parameters, both subjective and objective should be used to define cure. Since incontinence itself is multidimensional then its assessment also should be an include the outcome of objective testing, subjective assessments by the patient and also a measure of quality of life. The importance of these outcome variables has recently been investigated amongst patients, nursing staff and medical staff (Tincello and Alfirevic, 2002). Subjective improvement and improvement in quality of life were rated most highly amongst all groups and the authors go on to recommend that these be used as primary outcome measures in future clinical trials. Whilst this is certainly a pragmatic solution clinically objective measures of outcome such as urodynamics, pad tests and urinary diaries still allow us to decide which treatment is better or more effective in the research setting.

Outcome data is also further complicated by the variables used in its assessment; whom to measure and what to measure? This has recently been illustrated by the results of the tension-free vaginal tape (TVT) and colposuspension trial (Ward and Hilton, 2002) where objective cure rates were found to differ significantly depending on the population studied. Using a true intention-to-treat (ITT) population cure rates were 66% and 57% in the TVT and colposuspension arm respectively. If those who withdrew from the study following randomisation are discounted this 'modified ITT' analysis reveals objective cure rates of 68% and 66% respectively. However, using a more conventional per protocol

(PP) analysis results in an objective cure of 79% for both procedures (Hilton, 2002).

If we decide whom to measure it then leaves the problem of what to measure. Depending on the outcome variable used cure rates in the TVT and colposuspension trial vary between 9% and 81% for TVT and 6% and 68% for colposuspension. Using the most strict definition of cure, defined by the National Institutes of Health (NIH) as 'the resolution of the symptom and sign of stress incontinence and the absence of new symptoms or side effects' (Weber *et al.*, 2001)¹⁰ then cure rates were 9% for TVT and 6% for colposuspension. Whilst this may be scientifically correct it is doubtful whether such a definition would be clinically useful to clinicians or patients.

At present there is no consensus amongst clinicians, professional bodies and publications regarding the definition of cure and how it should be used as an endpoint in clinical trials. The small study presented in this thesis confirms a lack of conformity of clinicians in the United Kingdom, all of whom are members of ICS (UK). Ultimately patient satisfaction is perhaps the most important clinically although objective measures will continue to have a role in research.

Desmopressin in the Management of Daytime Urinary Incontinence

Until relatively recently drug therapy has been used predominantly in women complaining of symptoms of urge incontinence or overactive bladder syndrome. The development of duloxetine has, for the first time, provided an alternative to surgery in those women with stress incontinence. Pharmacological therapy, whilst not offering a permanent and definitive solution, does have the advantage of being reversible and lacks the morbidity and mortality associated with surgery.

The findings of the exploratory study reported in this thesis suggest that desmopressin offers a safe and effective treatment modality in women complaining of daytime urinary incontinence of mixed aetiology. The ability to choose when to self-administer medication leads to empowerment and as such may improve compliance. In addition, since our findings suggest that some women are reluctant to take regular medication for lower urinary tract dysfunction this may offer a suitable compromise to be used as and when required.

Antimuscarinic drugs are associated with the troublesome side effects of dry mouth, constipation, somnolence and blurred vision and this is known to affect compliance. Consequently the availability of an alternative drug therapy is attractive and may be

particularly useful in those women who are unable to tolerate anti-muscarinics or duloxetine.

More recently the efficacy of antimuscarinic agents has also been questioned in a large meta-analysis including 32 trials and 6800 patients (Herbison *et al.*, 2003). At the end of treatment cure or improvement (RR 1.41; 95% CI 1.29-1.54), differences in incontinent episodes in 24 hours (RR 0.6; 95% CI 0.4-0.8) and number of voids in 24 hours (RR 0.6; 95% CI 0.4-0.8) were all significantly better in those patients taking antimuscarinic drugs ($p < 0.0001$). However, despite significant statistical findings the authors question the clinical benefit of such small changes in outcome measures; statistical significance does not always translate into clinical and therapeutic significance.

Overall those subjects taking antimuscarinics were significantly more likely to be subjectively improved, had fewer episodes of incontinence and also had reduced frequency of micturition. Whilst this only equated to one less episode of incontinence and one less void over a 24-hour period this can be clinically relevant, particularly in terms of quality of life evaluation. When considering diurnal frequency, which is defined as 8 or more voids per day, a change from 12 to 11 voids per day would represent a reduction of 25% of the excess voids. The same would not be true for urinary incontinence episodes which most women would like to reduce to zero. Whilst meta-analysis is valuable as a tool for evidence based medicine although we should be wary that, by looking at the evidence too closely, we ignore a therapeutic effect that leads to subjective clinical improvement in bothersome lower urinary tract symptoms.

Although this study of desmopressin was only exploratory in nature it shows that a self-administered anti-diuretic agent is effective in the management of women with troublesome daytime symptoms. These findings would be supported by a larger, appropriately powered study comparing the use of desmopressin with either regular, or as required, anti-muscarinic agents. As an additional outcome variable QoL should also be assessed using a disease specific quality of life instrument and this would be in keeping with ICS guidelines when evaluating a new method of treatment. Patient satisfaction may also offer an alternative measure of outcome assessment and, since this approach is highly patient orientated, would provide an accurate appraisal of the management strategy.

In keeping with all pharmacological studies in women with lower urinary tract dysfunction there was a relatively high placebo response rate in this study. This is due to the increased level of clinical input inherent in all clinical trial situations as well as the biofeedback and bladder retraining effect of

keeping patient diaries. The use of an electronic diary provides an alternative to traditional paper diaries although this is unlikely to remove this potential source of bias completely.

As with all drug therapy adverse effects may limit clinical usefulness and the development of a shorted acting anti-diuretic agent with less theoretical risk of hyponatraemia and water intoxication may improve the safety profile, although this was not found to be a concern in this study.

Final Conclusions

The management of women complaining of urinary incontinence and lower urinary tract dysfunction is becoming increasingly consumer led and patient driven with a move away from the use of objective measures of assessment and cure. This thesis has demonstrated that desmopressin is safe and effective and may be used as a self-administered 'designer' therapy for women complaining of daytime urinary incontinence who may not be suitable for a more conventional approach to their lower urinary tract symptoms.

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