

A Randomized, Double-Blind, Placebo-controlled Crossover Trial of Nimodipine for Geriatric Urge Incontinence

by

Christopher David Brymer
838021920

A thesis submitted in conformity with the requirements of the degree of Masters of Science in Clinical Epidemiology, Graduate Department of Community Health, University of Toronto

©Copyright by Christopher David Brymer (1997)

The author has granted a non-exclusive licence allowing the National Library of Canada to reproduce, loan, distribute or sell copies of this thesis in microform, paper or electronic formats.

The author retains ownership of the copyright in this thesis. Neither the thesis nor substantial extracts from it may be printed or otherwise reproduced without the author's permission.

L'auteur a accordé une licence non exclusive permettant à la Bibliothèque nationale du Canada de reproduire, prêter, distribuer ou vendre des copies de cette thèse sous la forme de microfiche/film, de reproduction sur papier ou sur format électronique.

L'auteur conserve la propriété du droit d'auteur qui protège cette thèse. Ni la thèse ni des extraits substantiels de celle-ci ne doivent être imprimés ou autrement reproduits sans son autorisation.

0-612-29205-3

A Randomized, Double-Blind, Placebo-controlled Crossover Trial of Nimodipine for Geriatric Urge Incontinence

M.Sc. Thesis, 1997

Christopher David Brymer

Department of Community Health

University of Toronto

Abstract

This randomized controlled crossover trial evaluated the efficacy of nimodipine for geriatric urge incontinence. Eighty-six participants with irreversible geriatric urge incontinence, who met inclusion criteria were randomized to receive nimodipine, or placebo during the first treatment period. Participants received 30 milligrams of nimodipine twice daily for three weeks, and matched placebo twice daily for three weeks, separated by a two week washout period. The primary outcome was number of incontinent episodes, as measured by self completion of a five day voiding record. Secondary outcomes included questionnaires assessing other urinary symptoms, and the psychosocial impact of urinary incontinence.

Seventy-six participants completed the study. There was no significant difference in number of incontinent episodes with nimodipine versus placebo (.03 fewer incontinent episodes with placebo, $p = .965$, 95% confidence intervals -2.7 to 2.7 incontinent episodes over the five day voiding record). Scores on the Incontinence Impact Questionnaire and the American Urologic Association Benign Prostatic Hypertrophy Symptom Score were not significantly different with nimodipine versus placebo ($P = .068$, and $.215$, respectively).

Based upon the lack of a significant improvement in voiding records, urinary symptom scores, or psychosocial impact of urinary incontinence, nimodipine is ineffective for the treatment of geriatric urge incontinence.

Acknowledgements

This research was funded in part by Physicians' Services Incorporated, and Miles Canada.

I would like to thank:

Gary Naglie, for quiet support, insight, humour, and above all, the consistently outstanding teaching and advice that has been a key part of my growth as a doctor and a person;

Allan Detsky, for support, guidance and encouragement through what has been a prolonged, but rewarding adventure;

Maria Zorzitto, for both the inspiration and clear-eyed skepticism necessary to undertake this type of research;

Keith O'Rourke for patience and statistical advice and understanding and patience;

Sidney Radomski and Karen Mathiasen for their amazing devotion and outstanding work in completing this trial;

my wife Susan, son Matthew, daughter Rachel, and soon to be daughter Sarah, for their love, and tolerance of all the hours spent away from them.

Table of Contents

	<u>Page</u>
1 General Introduction	
1.1 Brief summary	1
1.2 Urinary incontinence - types and significance	2
1.3 Effective therapies for urge incontinence	3
1.4 Shortcomings of currently available therapies in a geriatric population	5
1.5 Rationale for the use of nimodipine to treat geriatric urge incontinence	6
1.6 Outcome measures in assessing treatments for geriatric urge incontinence	8
1.7 Study designs in assessing treatments for geriatric urge incontinence	10
2 Primary and secondary hypotheses	12
3 Research Design and Methods	
3.1 Study design and administration	13
3.2 Sample specification/Recruitment	13
3.3 Baseline Data/ Run-in Period	15
3.4 Manoeuvre	17
3.5 Outcome Measures - Development and Collection	18
3.6 Sample size justification	20
3.7 Statistical analysis	21
3.8 Funding	26
3.9 Ethical considerations	26
4 Results	
4.1 Study profile/Baseline characteristics	28
4.2 Voiding records	30
4.3 Incontinence Impact Questionnaire (IIQ)	35
4.4 American Urologic Association Symptom Score (AS)	38
4.5 Effect of age and sex upon the 3 major outcome measures	40
4.6 Adverse effects	42
4.7 Compliance	44
4.8 Maintenance of double-blinding	45
5 Discussion	
5.1 Methodologic issues regarding data analysis in crossover trials	46
5.2 General	49
6 Conclusions	55
7 References	56

8 Appendices

A Baseline Incontinence History, Medical History and Physical Examination	63
B Cystoscopic and Urodynamic Evaluation	70
C Voiding Record	72
D Incontinence Impact Questionnaire	73
E American Urologic Association Symptom Score	75
F Adverse Effects Questionnaire	77
G Clinical Information Sheet/Informed Consent Form	78

<u>List of Tables</u>	<u>Page</u>
Table 1- Baseline Characteristics of Randomized Participants	29
Table 2 - Baseline Characteristics of Randomized versus Non-randomized Participants	30
Table 3 - Total Number of Incontinent Episodes, By Group and Period	31
Table 4 - Daytime and Nocturnal Voiding and Incontinent Episodes, Nimodipine versus Placebo	34
Table 5 - Incontinence Impact Questionnaire (IIQ17) Summary Score, by Group and Period	37
Table 6 - American Urologic Association Symptom Score (AS), by Group and Period	39
Table 7 - Responses to Adverse Effects Questionnaire	43

List of Figures

Figure 1 Study Design	16
Figure 2 Treatment, Period, and Carryover Effects in a Crossover Trial	22
Figure 3 Treatment, Period, and Carryover Effects in a Crossover Trial with Baseline Measurements	23
Figure 4 Results of a simulation to compare analytic techniques for a crossover trial	25
Figure 5 Study Profile	28
Figure 6 Total Number of Incontinent Episodes, Mean and 95% Confidence Intervals, by Group and Period	31
Figure 7 Total Number of Incontinent Episodes, by Individual, Periods 1 and 2, for Group 1 (left) and Group 2 (right)	32
Figure 8 Number of incontinent episodes with placebo minus number of incontinent episodes with nimodipine versus Number of incontinent episodes during Run-in B, by Individual	35
Figure 9 IIQ17 Summary Score, Mean and 95% confidence intervals, By Group and Period	37

1 Introduction

1.1 Brief Summary:

The purpose of this randomized controlled double-blind crossover clinical trial was to determine the efficacy of the calcium channel blocker nimodipine, at a dose of 30 mg twice daily, in treating urinary urge incontinence in a geriatric outpatient population. Participants were 65 years of age and older with history, physical examination and urodynamic findings consistent with urge incontinence. The primary outcome measure was the change in the number of incontinent episodes, as measured by a voiding record completed by the patient. Secondary outcome measures include the documentation of adverse effects attributable to nimodipine, and the effect of nimodipine upon other urinary symptoms, and disease specific quality of life.

My role in this clinical trial consisted of:

- 1) development of the protocol, including literature review, study design, sample size calculation, choice of statistics for data analysis, choice and development of outcome measures and development of data collection forms;
- 2) provision of some of the training of the research assistant, who collected most of the data and performed data entry;
- 3) participation in the setup and initiation of the clinical trial;
- 4) data analysis.

1.2 Urinary incontinence - types and significance

Urinary incontinence is a common condition, affecting 15 to 30% of all community dwelling persons over the age of 60, and 50% of all nursing home residents.^{1,2} It is a disabling condition, causing shame, embarrassment, social isolation, decreased activity and loss of independence, and is a major factor in the institutionalization of frail elderly.³ In addition, urinary incontinence can lead to major medical complications, including pressure sores, the need for indwelling urinary catheters, urinary tract infections, and death. The direct cost of urinary incontinence in adults in the United States in 1987 was over 10 billion dollars, exceeding the budgets for coronary artery bypass grafting and hemodialysis combined.⁴

Urinary incontinence in community-dwelling elderly is most commonly due to urge incontinence (UI), stress incontinence, or overflow incontinence. Stress incontinence refers to the predictable leakage of small urine volumes with laughing, sneezing, or coughing, and is the second most common cause of incontinence in elderly women. Overflow incontinence refers to the unpredictable leakage of variable amounts of urine secondary to an obstruction to the outflow of urine, usually due to an enlarged prostate gland, and is the second most common cause of incontinence in elderly men. Urge incontinence is defined as urinary incontinence associated with a strong urge to void (urgency), with evidence of detrusor muscle instability or hyperreflexia documented by urodynamic testing. UI can occur either alone or in combination with bladder outlet obstruction in elderly men or bladder outlet incompetence (stress incontinence) in women.⁵ Correction of concomitant bladder outlet obstruction or incompetence will frequently lead to resolution of UI.^{6,7} There are many reversible causes of UI, including fecal impaction and local bladder irritation due to tumor, infection or stones. However, the majority of cases of UI are

nonreversible, and are felt to be due to the loss of tonic inhibition of detrusor contractions. This loss of inhibition can occur secondary to a wide variety of neurologic conditions, including Parkinson's disease, stroke, dementia, delirium, autonomic neuropathy, or spinal cord injuries. For many patients with established geriatric urge incontinence, no underlying cause can be identified. Urge incontinence is the most common cause of incontinence in both elderly men and women. It causes the leakage of large volumes of urine, and hence has a major impact upon quality of life in the elderly; urge incontinence is a common contributor to decreased activity, social isolation, depression, and long-term care placement in the elderly.¹¹

1.3 Effective therapies for urge incontinence

Both behavioural and pharmacological interventions have proved effective in the management of urge incontinence, while surgical approaches have been generally unsuccessful. Bladder training and pelvic muscle rehabilitation are the two best studied behavioural interventions for UI. Bladder training requires the patient to suppress the urge to urinate, voiding instead according to a timetable at progressively longer and longer intervals; it has been shown to reduce incontinent episodes in over 80% of patients with UI in one randomized trial, with similar effectiveness in several uncontrolled trials.^{8,9,11} Pelvic muscle rehabilitation teaches the patient to inhibit detrusor and abdominal contraction and to enhance pelvic muscle contraction when detrusor contraction occurs; it has resulted in a 75% or greater reduction in incontinent episodes in 6 uncontrolled trials.¹¹ However, in cognitively impaired patients, behavioural training is less effective, with only an 11% reduction in incontinent episodes noted in two studies of nursing home patients.^{10,11} Prompted voiding every two hours, wherein the cognitively impaired patient is

asked if he/she needs to void, and is assisted to the bathroom if necessary, reduced incontinent episodes 48% in a randomized controlled trial (RCT) involving 46 nursing home patients.¹²

A wide variety of pharmacologic agents have shown efficacy in at least one RCT for the treatment of UI. These agents can be classified as primarily anticholinergic (propantheline, tricyclic antidepressants), primarily smooth muscle relaxant (calcium channel blockers such as flunarazine), or possessing both properties (oxybutynin, terodiline, dicyclomine). Five RCTs evaluating propantheline (three in nursing home patients) have shown modest (mostly less than 20%) reductions in incontinence frequency, with only occasional cure (less than 15%).¹⁴⁻¹⁸ The results of three RCTs performed with tricyclic antidepressants have shown significant decline only in nocturnal incontinence.^{13,19,20} Flunarazine significantly reduced the number of incontinent episodes in one RCT involving 14 patients in a crossover trial, although this effect was diminished in a follow-up trial.^{21,22} Five of the seven RCTs involving terodiline have demonstrated a significant reduction in incontinence frequency (range 14 to 50%), as have 5 of 6 RCTs involving oxybutynin (range 15 to 56%).^{18,23-34} In two RCTs evaluating dicyclomine, reduction in incontinence frequency averaged 44%.^{15,35} Higher cure rates have generally been noted in trials involving predominantly younger patients at higher doses. Of the six RCTs showing no efficacy of drug treatment (involving oxybutynin, propantheline, terodiline, and imipramine), three were restricted to geriatric populations.^{13,17,30} Average reduction in incontinence frequency, based on the 12 RCTs which exclusively evaluated either younger (less than 65 years of age) or older (over 65 years of age) subjects, were 24% and 11%, respectively.^{13,16-18,23,25-30,33} Urodynamic studies in subjects who were taking medications which proved to be effective have shown that involuntary contractions are only rarely abolished by drug therapy.^{19,27,28}

1.4 Shortcomings of currently available therapies in a geriatric population

The currently available drugs for treating UI all have significant side effects which severely limit their use in a geriatric population. Anticholinergic side effects, most commonly dry mouth, blurred vision, constipation, nausea, confusion, dry skin, and fatigue were reported by approximately 30% of younger patients (less than 65 years of age) and 60% of older (more than 65 years of age) in RCTs of propantheline, tricyclic antidepressants, and oxybutynin.¹¹ At six month follow-up, Tapp et al found that less than half of 21 post-menopausal patients who had responded to oxybutynin were still taking the medication, while all who continued to take oxybutynin did so at reduced doses due to side effects.³² Oxybutynin frequently causes confusion and delirium in elderly patients, even at moderate doses.³⁰ Terodiline has not been approved by the Food and Drug Administration, due to recent reports of its association with severe ventricular arrhythmias.¹¹ Flunarizine has been shown to have antidopaminergic properties in addition to causing calcium channel blockade, and has caused Parkinsonism in several elderly patients.³⁶

The effectiveness of behavioural therapy has predominantly been demonstrated in younger (aged 40 to 65), highly motivated individuals.¹¹ It is a labor-intensive intervention, involving approximately 20 hours of one-to-one teaching of the patient, and often takes several months to achieve improvement.^{11,37} The training of nurses or other health care personnel such that they can provide this therapy to patients is similarly time-consuming. Elderly patients with UI frequently have mild cognitive impairment, and are therefore less likely to benefit from behavioural therapy, due to poor carry-over.

1.5 Rationale for the use of nimodipine to treat geriatric urge incontinence

Nimodipine is a dihydropyridine calcium channel blocker which relaxes both vascular and nonvascular smooth muscle. It has been extensively evaluated in patients with subarachnoid hemorrhage, and has reduced mortality and improved neurologic outcome in this setting.³⁸ It is postulated that nimodipine may enhance collateral circulation to underperfused areas of the brain via dilation of small arterioles.^{39,40} Nimodipine is currently approved as a limited use product for the treatment of subarachnoid hemorrhage in Ontario. Nimodipine has also been evaluated as a cognitive enhancer, and has accelerated learning in older rabbits, improved memory in older rats, and has significantly slowed functional decline in a short-term study in elderly humans with primary degenerative dementia.⁴¹⁻⁴³ Electroencephalographic (EEG) studies in 10 elderly patients with minor cognitive impairment suggest that nimodipine improves vigilance with a 40 mg oral dose.⁴⁴ Other studies have shown nimodipine to be a potent smooth muscle relaxant within temporal arteries and the lower esophageal sphincter.^{45,46} Nimodipine may act centrally to enhance cognition and/or vigilance, or may improve perfusion to underperfused areas of the brain which may play a role in inhibiting detrusor contractions. The central inhibitory control centre for bladder contractions has been localized to the frontal lobes bilaterally, in the areas overlying the lateral ventricles.⁴⁷ McCracken et al have demonstrated hypoperfusion of this area by SPECT scan in a large series of geriatric patients with urge incontinence.⁴⁸

Elliot et al have recently published the results of several experiments comparing the effects of the calcium channel blockers nifedipine, nimodipine, and verapamil upon contraction of the detrusor muscle in vivo, using rat and human bladder tissue.⁴⁹ In their studies, nimodipine was a far more potent inhibitor of detrusor contractions than either nifedipine or verapamil, in both rat

and human bladder tissue. The concentrations of nimodipine in vivo that inhibited detrusor contractions in human bladder tissue (.1 umol/L) are far less than the peak serum levels achieved in volunteers who took a single 30 mg oral dose (.6-1.5 umol/L).⁵⁰ The elimination half life for nimodipine is approximately 8 hours.⁵⁰ It is therefore highly plausible that nimodipine at a dose of 30 mg twice daily may have a beneficial effect in UI. Nifedipine, a dihydropyridine calcium channel blocker similar to nimodipine, has been shown to diminish detrusor contractions and frequency of incontinence in one uncontrolled trial involving 10 women with urge incontinence.⁵¹ Nifedipine is a potent antihypertensive medication, in addition to causing frequent edema and constipation in elderly patients; it is, therefore, useful only for treating geriatric incontinence in hypertensive patients. Unlike nifedipine, nimodipine has minimal effect on blood pressure.

Nimodipine has been remarkably free of side effects in the trials cited above. A 5% incidence of hypotension was noted in a meta-analysis of seven studies of nimodipine therapy for subarachnoid hemorrhage (at doses from 360 to 540 mg/day, far higher than in the current study), while no other adverse effects were noted more frequently than with placebo.³⁸ In Tollefson's study, no hypotension was noted in 70 demented elderly patients receiving 90 mg/day, and no other adverse events were noted in excess of placebo.⁴³

There are two possible mechanisms whereby nimodipine may ameliorate UI in this population. It may act directly on detrusor smooth muscle to diminish bladder tone and/or decrease frequency and strength of uninhibited detrusor contractions. Alternatively, nimodipine may act centrally to enhance cognition and/or vigilance, or may improve perfusion to underperfused areas of the brain which may play a role in inhibiting detrusor contractions. Given the potential beneficial effects at both the level of the bladder and the brain, it is a reasonable

agent to evaluate for efficacy in treating geriatric urge incontinence, which is a common, disabling and expensive condition.

1.6 Outcome measures in assessing treatments for geriatric urge incontinence

The outcome measure most commonly used in assessing treatments for UI has been simple, ie the single item subjective report by the patient that their urinary incontinence is better, worse, or cured. As an outcome measure, such a report is not standardized, and may have poor reproducibility.⁵² Voiding records,(VRs) wherein patients record every continent and incontinent episode over a specified length of time, usually one to seven days, are an alternative outcome measure with greater face validity. VRs have been validated, and shown to have a test-retest reliability of .89 at one week in patients with urge incontinence.⁵³ The VR has been recommended by a recent clinical practice guideline panel as a useful measure for determining incontinence severity and treatment efficacy.¹¹ Norton, however, has noted poor correlation between the frequency of incontinence and the self-perceived effect of urinary incontinence upon mental well-being, day-to-day activities, and relationships with friends and family.⁵⁴

Wyman et al subsequently developed and validated the Incontinence Impact Questionnaire (IIQ), which qualitatively and quantitatively describes the quality of life impact attributable to incontinence.⁵⁵ Construct and criterion validity for the IIQ have been demonstrated in a sample of perimenopausal women predominantly suffering from a mix of stress and UI, by examining correlations with various generic health-related quality of life and psychological measures, and by examining correlations with number of incontinent episodes, respectively.^{9,56}

The American Urological Association Benign Prostatic Hypertrophy symptom score (AS)

has been shown to be reliable ($r=.93$ on test-retest one week apart), with reasonable construct and criterion validity, and sensitivity to change in elderly men receiving treatment for benign prostatic hypertrophy.⁵⁷ The AS has recently been shown to be valid and reliable in postmenopausal women with stress and urge incontinence as well.⁵⁸ The AS differs from both the IIQ and the VR, in that it asks the patient to semiquantitatively describe a number of urinary symptoms, including incontinence. The IIQ and the AS have never been compared to each other, and neither has been used to measure responses to drug therapy for geriatric UI, hence their sensitivity for our usage is unknown. Nevertheless, they represent the best currently available measures for UI. It is likely that the VR, AS, and the IIQ are measuring distinct, but related and clinically important aspects of UI, specifically the number of incontinent episodes, other urinary symptoms, and the impact of both upon quality of life, respectively.

Although urodynamic evaluation is very helpful in differentiating UI from overflow or stress incontinence, there is considerable debate regarding the correlation between urodynamic and symptomatic response to pharmacologic therapy.¹¹ Reliance upon urodynamic testing as an outcome measure may misrepresent the response to treatment in two ways. First, it is common for symptomatically improved patients in incontinence drug trials to have persistent detrusor overactivity on urodynamic testing; this would lead to an underestimation of response to therapy in these patients.¹¹ Second, urodynamic improvement can occur without a decrease in the number of incontinent episodes⁵⁹; reliance upon urodynamic testing as an outcome measure would then overestimate the benefit of the pharmacologic intervention. For the above reasons, and a desire to avoid invasive procedures where possible, urodynamic testing is not used as an outcome measure in this study.

1.7 Study designs in assessing treatments for geriatric urge incontinence

Previous studies of drug treatments for UI have frequently demonstrated fairly high placebo response rates, which would argue strongly for the use of RCT study design to accurately determine the magnitude of any treatment effect. UI is typically a chronic condition with only modest fluctuations in symptoms on a day-to-day basis. Different patients, however, can have vastly different symptomatology, with large ranges in urinary frequency, number of incontinent episodes, and impact upon quality of life. The degree of symptom improvement within a particular patient may be much smaller than the difference in symptoms between patients, even with a highly effective intervention. Allowing each patient to serve as their own control, in a crossover RCT, should provide greater power to detect a treatment effect than would a simple RCT. Therefore, a crossover RCT will allow detection of a treatment difference with a much smaller sample size than a standard RCT. This would be a major benefit, since previous RCTs of drugs for UI, with few exceptions, have been unable to recruit more than 50 patients.

Jones and Lewis have recently described situations in which crossover trials are not recommended:

- i) diseases where the primary measurement is an event such as death, infarction, cancer recurrence, or cure of infection;
- ii) unstable diseases such as hay fever, unstable angina and schizophrenia;
- iii) diseases where gradual deterioration, such as that observed with AIDS, multiple sclerosis and heart failure, is expected;
- iv) those situations where a long treatment period is needed, such as with mild angina and mild migraine, in order to observe enough attacks;

v) situations where there is a high incidence of adverse reactions; and

vi) situations where a high dropout rate is expected.⁶⁰

As UI is a chronic, stable disease, which should respond quickly to an effective medication, with few adverse effects or dropouts, use of a crossover trial study design seems reasonable. An important assumption in the use of a crossover study design is that subjects return to baseline values for outcome measures at the end of the washout period, ie, before beginning the second treatment period.

2 Primary and secondary hypotheses

Study Question/Primary hypothesis: treating urge incontinence in a geriatric outpatient population with nimodipine will significantly decrease the number of incontinent episodes.

Secondary hypotheses:

1) treatment with nimodipine will significantly improve disease specific quality of life and other urinary symptoms in patients with geriatric urge incontinence, as measured by two measures (the modified Incontinence Impact Questionnaire (IIQ), and the American Urologic Association Benign Prostatic Hypertrophy Symptom Score(AS)) that have not previously been validated in elderly patients with urge incontinence. The nested hypothesis is that these questionnaires will be shown to be valid and reliable in this population.

2) nimodipine will be safe and well tolerated in three respects:

- a) it will cause no more adverse effects than placebo;
- b) it will have no significant effect upon the postvoiding residual urine volume compared to placebo (ie, it will not cause urinary retention);
- c) it will have no significant effect upon blood pressure compared to placebo.

These hypotheses were specified before looking at the actual data.

3. Research Design and Methods

3.1 Study design and administration

This study was a randomized, double-blind, placebo-controlled crossover trial, whose recruitment, randomization, data collection, and statistical analyses were monitored by a steering committee consisting of the study investigators (Gary Naglie, Sid Radomski, Chris Brymer), the research assistant (Karen Mathiassen), and the study biostatistician (Keith O'Rourke).

3.2 Sample specification/Recruitment

Eligible patients were all patients seen at the Toronto Hospital Geriatric Incontinence Clinic, either by physician referral or after telephone inquiry, whose history, physical examination, urodynamic and cystoscopic evaluations were consistent with nonreversible urge incontinence, and who met the inclusion and exclusion criteria outlined below. Strict exclusion criteria were used to make the study population as homogeneous as possible, in order to maximize power to demonstrate the efficacy of nimodipine, before considering an effectiveness trial, which would include a more heterogeneous population. Reliance upon the combination of history, physical examination and urodynamic data to diagnose geriatric UI is the most reliable and valid method currently available.¹¹ Instability or hyperreflexia on urodynamic testing will be defined, in accordance with the International Continence Society, as a rise in detrusor pressure greater than or equal to 15 cms of water. Urge incontinence will be defined as urinary leakage with bladder instability or hyperreflexia. Recruitment was enhanced by providing information regarding the study to local urologists, gynecologists, geriatricians, and family physicians, and by newspaper articles, radio and television interviews, and posters in family physicians' offices.

Inclusion Criteria:

- 1) Greater than or equal to 65 years of age.
- 2) Involuntary loss of urine on at least four occasions over a five day period, documented on a voiding record.
- 3) Provision of informed consent.

Exclusion Criteria:

- 1) Post-void residual urine volume of greater than 100 cc's at the time of urodynamic testing, indicating the patient may be at increased risk for developing urinary retention with nimodipine.
- 2) Patients with cystoscopic or urodynamic evidence of outlet obstruction (ie, benign prostatic hypertrophy, urethral stricture).
- 3) Urine leakage that occurred with coughing while supine at the time of urodynamic testing, suggesting moderate to severe stress incontinence.
- 4) Patient currently on a calcium channel blocker.
- 5) Patient has prostate or bladder cancer noted at cystoscopy, which could cause persistent detrusor instability
- 6) Patient has a positive urine culture, suggestive for a urinary tract infection, and urinary incontinence resolves with antibiotic therapy.
- 7) Patient has insulin-dependent diabetes, or spinal cord pathology, and hence is likely to have neurogenic bladder dysfunction.
- 8) Patient has symptomatic orthostatic hypotension, overt congestive heart failure, or ventricular arrhythmias requiring suppressive medication.
- 9) Patient has cognitive impairment, as demonstrated by a score of <24/30 on a Folstein Mini-

Mental State examination, as patients with this degree of cognitive impairment are unlikely to comply with completion of the primary outcome measure.⁶¹

10) Inability to complete a voiding record during the second week of the run-in period.

11) Patient requires indwelling catheter, condom, or intermittent catheterization at the time of assessment.

3.3 Baseline Data/Run-in Period

Baseline Data

A medical history (including baseline incontinence history) and physical examination (Appendix A)

Lying and standing blood pressure.

Urinalysis, urine culture.

Urodynamic testing, including stress manoeuvres and determination of postvoid residual urine volume(Appendix B)

Cystoscopy(Appendix B)

A Folstein Mini-mental state examination⁶¹

Voiding record (VR) - a patient generated diary of the number and timing of voluntary micturitions and incontinent episodes daily for five days (Appendix C)

Incontinence Impact Questionnaire (IIQ) - a 20 item self-administered questionnaire that measures the effect of urinary incontinence on psychosocial function in three broad areas - activities of daily living, social interactions, and self-perception (Appendix D)⁵³

American Urologic Association Benign Prostatic Hypertrophy Symptom Score (AS) - a seven

item, self-administered questionnaire that asks the patient to semiquantitatively describe several urinary symptoms, including incontinence (Appendix E)⁵⁷

Run-in Period (see figure 1 - Study Design)

Participants were educated by the research assistant during run-in periods A and B with regards to how to complete a voiding record, and how to complete the IIQ and AS. Voiding records, IIQ and AS were collected twice, 1 week apart during run-in periods A and B. Voiding records were reviewed by the research assistant with the patient during the run-in period for accuracy and completion. Prior to randomization, the research assistant again reviewed the participant's medications and medical history, and reviewed with the participant what their involvement in the study would entail.

Figure 1 - Study Design

	Run-in period A (1 week)	Run-in period B (1 week)	Period 1(3 weeks)	Washout (2 weeks)	Period 2 (3 weeks)
Group 1 - received nimodipine in period 1	day 1-6 - VR day 7-IIQ, AS	day 1-6 - VR day 7-IIQ, AS	day 15-20 -VR day 21 - IIQ, AS, Adverse effects questionnaire, repeat of selected baseline questions	day 8-13 -VR, day 14 - IIQ,AS, repeat of selected baseline questions	day 15-20 -VR day 21 - IIQ, AS, Adverse effects questionnaire, repeat of selected baseline questions
Group 2 - received nimodipine in period 2	day 1-6 - VR day 7-IIQ, AS	day 1-6 - VR day 7-IIQ, AS	day 15-20 -VR day 21 - IIQ, AS, Adverse effects questionnaire, repeat of selected baseline questions	day 8-13 -VR, day 14 - IIQ,AS, repeat of selected baseline questions	day 15-20 -VR day 21 - IIQ, AS, Adverse effects questionnaire, repeat of selected baseline questions

3.4 Manoeuvre (see figure 1 - Study Design)

Patients were enrolled in a stratified blocked fashion by sex and by age (greater than, or less than or equal to 70 years of age). Stratification by sex was undertaken because of the lack of published data regarding the response rates to therapies for urge incontinence in male patients, and to control for the possibility that male patients would respond in a systematically different manner. Stratification by age was undertaken because response rates to therapies have been lower in older patients in previous studies. Order of treatment was assigned via a computer-generated randomization code available from the study biostatistician, who provided coded bottles of medication for periods 1 and 2 to the research assistant. After the participant's code number was determined, he or she received a container of study medication containing either 45 capsules of nimodipine 30 mg, or placebo matched for appearance and taste. The participant was instructed to take one capsule every morning with breakfast and every evening before bedtime for three weeks (Period 1). The participant then returned the container with the unused portion of the medication to the research assistant, who performed a pill count to assess compliance. The maximum elimination half-life noted with nimodipine in prior studies was 22 hours, in 12 elderly subjects with varying degrees of renal failure.⁵⁰ Based on this information, a two week washout period was chosen, to ensure complete elimination, and collection of a 5 day voiding record was undertaken at the end of this washout period. After the washout period, the participant received a second container of study medication in a similar fashion with similar instructions, again with a repeat pill count after three weeks (Period 2).

3.5 Outcome Measures

Development

1) Adverse Effects Questionnaire (Appendix F) - all adverse effects reported to occur with nimodipine in any previous trial in more than 1% of participants were noted. In some cases, the adverse effects noted in other trials were laboratory abnormalities. In all cases, the most representative sign or symptom was chosen and included as an item on the adverse effects questionnaire for this trial. A Likert-type response scale was used to determine whether each adverse effect was noted more frequently or less frequently than usual. An open-ended question was added for participants to express concerns about adverse effects not addressed by the Likert-type questions.

2) IIQ - the original version of the IIQ was a self-administered 26 item questionnaire with a semi-objective elemental scale response (none/slightly/moderately/greatly). The test-retest reliability, done 1 week apart, in 69 women with stress incontinence, or a mix of stress and urge incontinence, was .73, when classified as a dichotomous variable (none/slightly, vs. moderately/greatly), with a reliability of .69 expected by chance alone.⁵³ This version of the questionnaire was then used to measure response to behavioural therapy in 82 women with stress incontinence, or a mix of stress and urge incontinence.⁹ The absolute change score in this group was .28 with a pooled standard deviation of .45, for a Guyatt's responsiveness statistic value of .62. Guyatt et al have suggested that a value less than 1 indicates that a health status measurement lacks sufficient responsiveness to be clinically useful.⁶² Because of concerns regarding both the reliability and the responsiveness of the IIQ, we made several modifications to the IIQ prior to use in this study:

- a) item reduction: for 9 of the 26 items, less than 15% of the participants in the previous study answered 'moderately or greatly'; these items, where subject matter overlapped somewhat, were combined.
- b) item addition: other studies have noted a significant impact of UI upon quality and quantity of sleep⁶³; a single question, "Does your urine problem prevent you from getting enough sleep?" was added.
- c) change to a semiquantitative elemental scale: the objective scaled response ' never/less than half the time/about half the time/more than half the time/always/doesn't apply to me' was used. This scale is very similar to the scaled response used by Barry et al in developing the AS, a questionnaire which has been shown to be sensitive, with much better reliability than the IIQ, albeit in a different population.⁵⁷
- d) three post-treatment questions were added, to assess change in number of incontinent episodes, amount of urine leakage, and severity of urinary urgency. Change in the number of incontinent episodes was added to validate the VR, while change in the amount of urine leakage and the severity of urinary urgency questions were added to capture symptoms that may not be captured by the VR, AS, or other IIQ questions.
- 3) AS - a single, global quality of life question was added to the AS, in response to a publication by Grimby et al, shortly prior to study commencement, demonstrating that urinary incontinence can affect the score on a global quality of life measure, the Nottingham Health Profile Questionnaire.⁶³ The item added ("If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?") was used with a seven-point Likert-type response scale, ranging from 'delighted'(0) to 'terrible'(6).

Collection

The following outcome measures were collected:

- 1) Selected items from the baseline incontinence history were repeated at the end of treatment periods 1 and 2, and at the end of the washout period; they are noted in bold in appendix A.
- 2) Five-day voiding records were collected at the end of period 1, the washout period, and period 2. Patients were reminded by the research assistant by telephone to complete the voiding record near the end of each time period.
- 3) The IIQ and AS were collected at the end of periods 1 and 2, and at the end of the washout period.
- 4) At the end of treatment periods 1 and 2 the following were carried out:
 - a) an adverse effects questionnaire was completed,
 - b) a post-void residual urine volume was measured by in and out catheterization, to assess for urinary retention.
 - c) lying and standing blood pressure were recorded, to assess for orthostatic hypotension.

3.6 Sample size justification

Previous trials of drugs for incontinence have rarely collected change in number of incontinent episodes as an outcome measure. It is far more common to qualify response to treatment as 'cured or improved' versus 'no change' or 'worse'. Placebo response rates (cured or improved) in other drug trials for incontinence have ranged from 0 to 65%, with most trials noting placebo response rates of less than 40%. For purposes of sample size calculation, response to treatment was categorized as a dichotomous variable. Assuming a 40% placebo response rate,

and a 60% response rate to nimodipine, with $\alpha = .05$, and power = .8, the number of subjects required to detect a treatment effect would be approximately 190 in a standard parallel randomized trial. Use of a crossover study design reduces the sample size to 95 subjects, with each subject serving as their own control, assuming:

- a) there is no period effect,
- b) there is no carryover effect, and
- c) there is no correlation between the likelihood of response to nimodipine and the likelihood of response to placebo in a single subject. If there is a correlation, then the sample size will be less than 95. The greater the correlation, the smaller the sample size; McNemar's test for correlated proportions is an accepted method for estimating the impact upon sample size of differences in proportional response rates between different treatments.^{64,65} Assuming a modest correlation of .25 between responses to nimodipine and placebo gives a minimum sample size of 72 subjects.

The study goal was to recruit 90 patients. The real power of this study to detect a treatment difference was expected to be much greater than 80%, as change in incontinent episodes would be treated as a continuous variable in data analysis.

3.7 Statistical Analysis

There has been substantial controversy in the literature regarding the appropriate methodology for undertaking the statistical analysis of the results of a two-period crossover trial.^{60,66-74} The controversy centres on the handling of a carryover effect (see figure 2). Whereas a period effect simply implies that there is a general trend over time, towards a greater or lesser response, for both treatments, a carryover effect implies that the difference between treatments is

influenced by the period in which the treatment was given. In the literature, a carryover effect has also been referred to as an order effect, sequence effect, or treatment-by-period interaction.

Figure 2 - Treatment, Period, and Carryover Effects In a Crossover Trial (adapted from Woods et al⁶⁶)

	Period 1	Period 2
Sequence 1 (drug first)	A1	B1
Sequence 2 (placebo first)	B2	A2

A = outcome with drug, B = outcome with placebo

Treatment Effect - compares (A1+A2) to (B1+B2), ie, response to drug vs. response to placebo. If there is a difference, it suggests a treatment effect.

Period Effect - compares (A1+B2) to (B1+A2), ie, response in period 1 vs. response in period 2. If there is a difference, it suggests a period effect.

Carryover Effect = (A1+B1) vs. (B2+A2)

Grizzle suggested a two step procedure to determine whether a significant carryover effect was present, starting with the between subjects comparison described above, A1+B1 versus B2+A2.⁶⁹ If this comparison is not significant at $P=.1$, Grizzle postulated that a significant carryover effect was unlikely to be present, and suggested that the data could then be analyzed as a simple within-subjects comparison, ie, is (A1-B1)+(A2-B2) different from zero by a one-sample test (the cross procedure). If, however, A1+B1 is significantly different from B2+A2 at $P=.1$, he postulates that a significant carryover effect may be present, and suggests that the data should only be analyzed as a parallel-design trial, using the first period data only, ie A1 versus B2(par procedure).

Willan and Pater and Willan have suggested an alternative to the use of first period data only in the analysis of a crossover trial in the presence of a carryover effect.^{68,74} They suggest

that the size of a carryover effect that is required to make parallel design analysis preferable is substantial, and unlikely to exist in most cases. They have suggested, assuming there can be no carryover effect without a treatment effect, the simultaneous use of the cross procedure and the par procedure, with correction for multiple comparisons, as an alternative method for determining whether there is a treatment effect; if a P value of less than .025 is found with either analysis, then the difference between treatments can be treated as significant (Willan test).

Jones and Kenward have noted that, in studies where baseline and washout measurements are made, a carryover effect can occur via two mechanisms (figure 3):

Figure 3 Treatment, Period, and Carryover Effects in a Crossover Trial with Baseline Measurements

	Run-in	Period 1	Washout	Period 2
Sequence 1 (drug first)	R1	A1	W1	B1
Sequence 2 (placebo first)	R2	B2	W2	A2

- 1) differential first order carryover, ie, $(W1-R1)$ vs. $(W2-R2)$, or
- 2) differential second order carryover, ie, $(A1-R1)+(B1-W1)$ vs. $(B2-R2)+(A2-W2)$

Jones and Kenward have suggested that if a significant difference (at $P = .1$) is noted with either 1) or 2) above, then a carryover effect exists, and the data should be analyzed as if it were a parallel randomized trial, ie $(A1-R1)$ vs. $(B2-R2)$ (ie, the par procedure with baseline measures).⁶⁷ They have suggested that use of this model increases the power to detect a carryover effect, but that power to detect a carryover effect remains less than power to detect a treatment effect. Willan, Willan and Pater, and Jones and Kenward have all noted that with increasing carryover effect, the power to detect a treatment difference declines. They all have argued:

- a) that in situations such as placebo-controlled trials, it is highly unlikely that a carryover effect can occur in the absence of a treatment effect, and
- b) that only positive carryover effects can occur, ie that a treatment in period 1 can enhance, but not prevent a response to treatment in period 2.

The literature does not provide a 'clear winner' with regards to the appropriate choice of a technique for analyzing the data in a crossover trial with baseline measures. To provide some direction regarding choice of an analytic technique, Keith O'Rourke, the study biostatistician, undertook a simulation similar to that previously described by Jones and Lewis⁶⁰, to compare the power of the cross procedure, the par procedure (with baseline measures), the Willan test and the Jones and Kenward test (use of the par procedure if the test for first order carryover is significant at $P=.1$, use of the cross procedure if it is not) to detect a treatment difference; a) in the absence of a carryover effect, and b), in the presence of a carryover effect of size equal to the size of the treatment difference. It was assumed that treatment effects were normally distributed, and that correlation between measures (voiding records, the primary outcome measure) was high (.9) at baseline, and declined at a predictable rate over time (.1/period).

Given these assumptions, the Willan test consistently provided the greatest power to detect a treatment difference in the absence of a carryover effect, at the expense of slightly diminished power, compared to the Jones test, to detect a treatment difference in the presence of a carryover effect as large as the treatment effect (see figure 4). All 4 techniques suffered from inadequate power to detect a treatment difference in the presence of a carryover effect as large as the treatment difference; the Jones test was the best of the lot, with power to detect a treatment difference that was ONLY 20 to 30% less, in the presence of a carryover effect, when using

typical values for beta of between .05 and .20.

Figure 4 Results of a simulation to compare analytic techniques for a crossover trial

	P (type I error rate)	Power to detect a treatment effect if no carryover	Power to detect a treatment effect if a carryover effect is present
cross procedure	.0494	.9542	.4251
par procedure	.0505	.6544	.6514
jones and kenward procedure	.0596	.9166	.7162
willan procedure	.0494	.9575	.6760

type I error rate for this simulation was set at .05. Expected power to detect a treatment difference was set at 95% (beta = .05).

Based upon this comparison, it was decided to use the Willan test as the test for the presence of a treatment difference. For the three major outcome measures in this study (the Voiding Record, Incontinence Impact Questionnaire, and American Urologic Association Symptom Score), the Jones and Kenward tests for first and second order carryover effects will also be performed. If there is any evidence of a significant carryover effect, it is likely that this trial will have insufficient power to either detect or rule out a treatment difference of moderate size.

Data analysis was performed using SPSS for Windows version 7.0. An interim analysis of the data was not performed as, at the time of study commencement, neither the condition nor the treatment were felt to be life-threatening. Given the small sample size of this trial, an interim analysis would also be exceedingly underpowered to detect toxicity. When concerns regarding toxicity were raised in the course of the study, a meeting of the Safety Committee was convened to undertake a blinded analysis to determine if any side effects were disproportionately distributed

(see section 3.9). Data analysis was on an intention to treat basis, with performance of a sensitivity analysis to determine whether major outcomes were significantly different with exclusion of, or assumption of worst or best outcomes for, participants who dropped out during the study.

3.8 Funding

This project received peer-reviewed funding from the Physicians' Services Incorporated (PSI) Foundation in 1993. Supplementary funding, to offset participant transportation costs, was obtained from Miles Canada, the manufacturer of nimodipine, in 1993. Miles Canada also supplied the study medication, and matched placebo, free of charge. Miles Canada had no role in determining the study design; support from Miles Canada was sought only after peer-reviewed funding had been obtained. PSI provided additional funding as an extension of the primary grant in 1994.

3.9 Ethical Considerations

This project was approved by the University of Toronto Ethics Committee in 1993. A clinical information sheet was given to all participants prior to study entry, along with a copy of the informed consent form (Appendix G). The names of the study participants were only retained while the study was ongoing, with subsequent data storage only by the subject's randomization code number.

Cystoscopic and urodynamic testing is invasive, but is done routinely as part of a complete incontinence evaluation in the Toronto Hospital Geriatric Incontinence Clinic. Measurement of a post-void residual urine volume is also invasive, but is commonly done after starting any drug

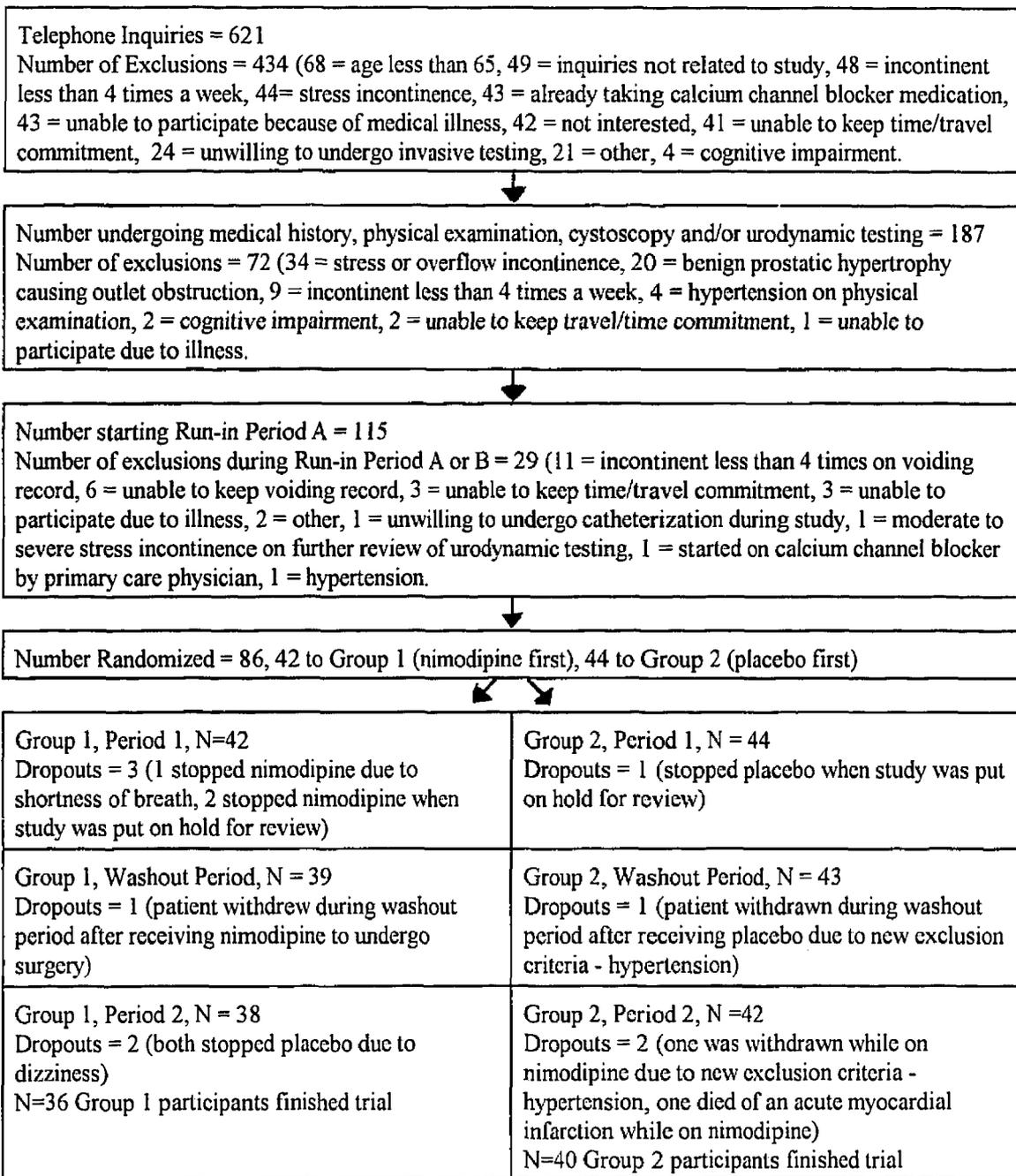
therapy for urge incontinence, as such drugs may induce urinary retention. We therefore felt that it was acceptable to include these procedures as part of the study. Patients who participated in the study were delayed at most 10 weeks from receiving 'standard therapy'. Waiting lists to be seen at the Toronto Hospital Geriatric Incontinence Clinic were 2 to 3 months at the start of the study, and did not change appreciably over the course of the study.

In late 1995, several cohort studies were published suggesting that short-acting calcium channel blockers like nimodipine may increase cardiovascular mortality in elderly persons taking calcium channel blockers, as opposed to other antihypertensive medications.^{75,76} In response to the literature, and the cardiac death of one participant in our study while receiving nimodipine, recruitment was temporarily suspended in November 1995. The Safety Monitoring Committee for this trial met in December 1995, and reviewed the recently published data and the adverse events that had occurred. They concluded that there was no evidence to support that nimodipine was causing more adverse events than placebo, and that there was very inconclusive evidence that patients with hypertension have an increased risk of adverse cardiac events when treated with calcium channel blockers. Their recommendation was to exclude patients with hypertension who had known coronary disease from this trial, and to revise the consent form in the light of the recently published data. The consent form was revised to include a paragraph about possible risks in patients with heart disease or high blood pressure (see paragraph 3, page 3, appendix G). Exclusion criteria for the trial were revised to exclude all patients with established coronary artery disease, as well as all individuals with established hypertension. The Toronto Hospital Ethics Committee renewed approval of the study given the above mentioned changes, and recruitment for the trial resumed January 15, 1996.

4 Results - 4.1 Study profile/Baseline characteristics

Six hundred and twenty-one telephone inquiries were received regarding the study; their disposition is displayed in figure 5.

Figure 5 - Study Profile



Baseline characteristics

The ten participants who failed to complete the study differed slightly from the 76 who did in age (69.5 versus 73.6 years), sex (90% versus 84% female), and number of incontinent episodes during the run-in periods (14.2 versus 18.2) ($P > .05$ for each).

Participants who were randomized were stratified by age (greater than 70 years of age versus less than or equal to 70 years of age) and sex. Table 1 demonstrates that stratification was successful, as participants who received nimodipine during period 1, and participants who received placebo in period 1 did not differ significantly in these respects. Age and sex of the 27 participants who dropped out during the run-in period are shown in table 2 (page 29); participants who dropped out during the run-in period were slightly older and significantly more likely to be male than were participants who were randomized. Of the 11 males who dropped out during the run-in period, 7 had an insufficient number of incontinent episodes (4 or less) on the 5 day voiding record, and 2 were unable to complete a voiding record.

Table 1 - Baseline Characteristics of Randomized Participants

	Participants who received nimodipine during period 1 (n = 42)	Participants who received placebo during period 1 (n = 44)	P
Sex	6 male, 36 female	7 male, 37 female	.917*
Age	73.3 years	73.5 years	.88#
Total number of incontinent episodes on pooled run-in voiding records	15.45	20.63	.139#
AS during run-in periods	13.73	14.92	.61#
IIQ score during run-in periods	21.05	23.04	.28#

* - chi-square

- independent sample t-test

Table 2 - Baseline Characteristics of Randomized versus Non-Randomized Participants

	Run-in Period Dropouts (n=27)	Randomized Participants (n=86)	P
Age	75.7 years	73.4 years	.179#
Sex	11 male, 16 female	13 male, 73 female	.017*
Total number of incontinent episodes on pooled run-in voiding records	9.8	18.06	.006#
AS during run-in periods	12.02	14.33	.276#
IIQ17 summary score during run-in periods	19.44	22.03	.191#

* - chi-square

- independent sample t-test

4.2 Voiding records

During the run-in period, two voiding records were completed by 98 participants.

Pearson correlation coefficient on the total number of incontinent episodes, run-in period A versus run-in period B was .768; when the analysis was limited to the 81 participants who went on to be randomized and completed two run-in period voiding records, Pearson correlation coefficient was much better at .915. The mean number of incontinent episodes during the run-in periods for participants who were not randomized (9.8) was significantly lower than for participants who were randomized, reflecting the insufficient severity of urinary incontinence in many of the participants who were excluded during the run-in period.

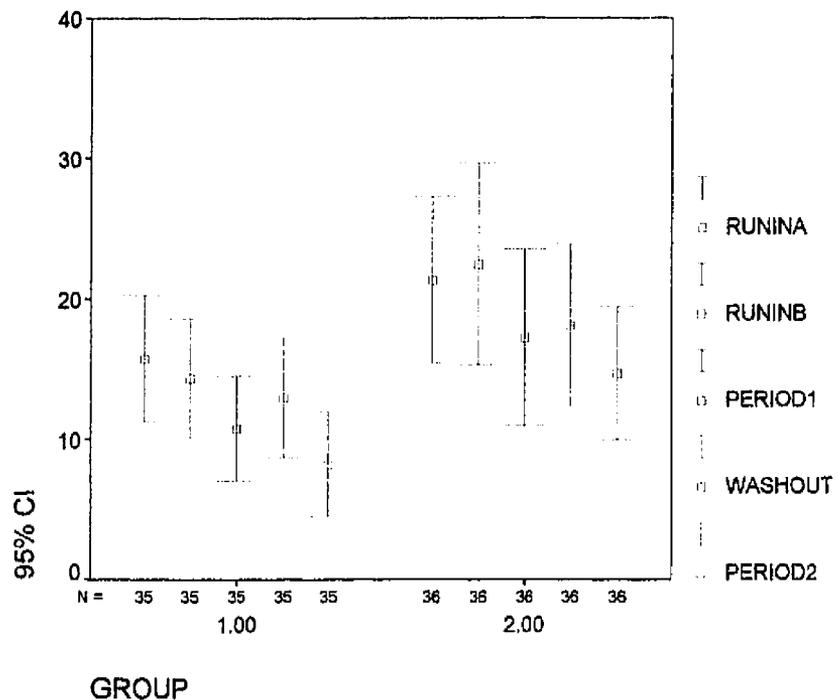
For the 86 participants who were randomized, the total number of incontinent episodes during each period are shown in table 3, and graphically in figures 6 and 7. There was a significant decline in the number of incontinent episodes over time, independent of the treatment given, suggestive for a period effect ($F=12.031$, $P<.001$ by GLM repeated measures; $F=.413$,

P=.796 for the addition of Group 1 versus Group 2 as a between subjects factor, suggesting that this change over time was independent of treatment given)

Table 3 - Total number of incontinent episodes, by group and period

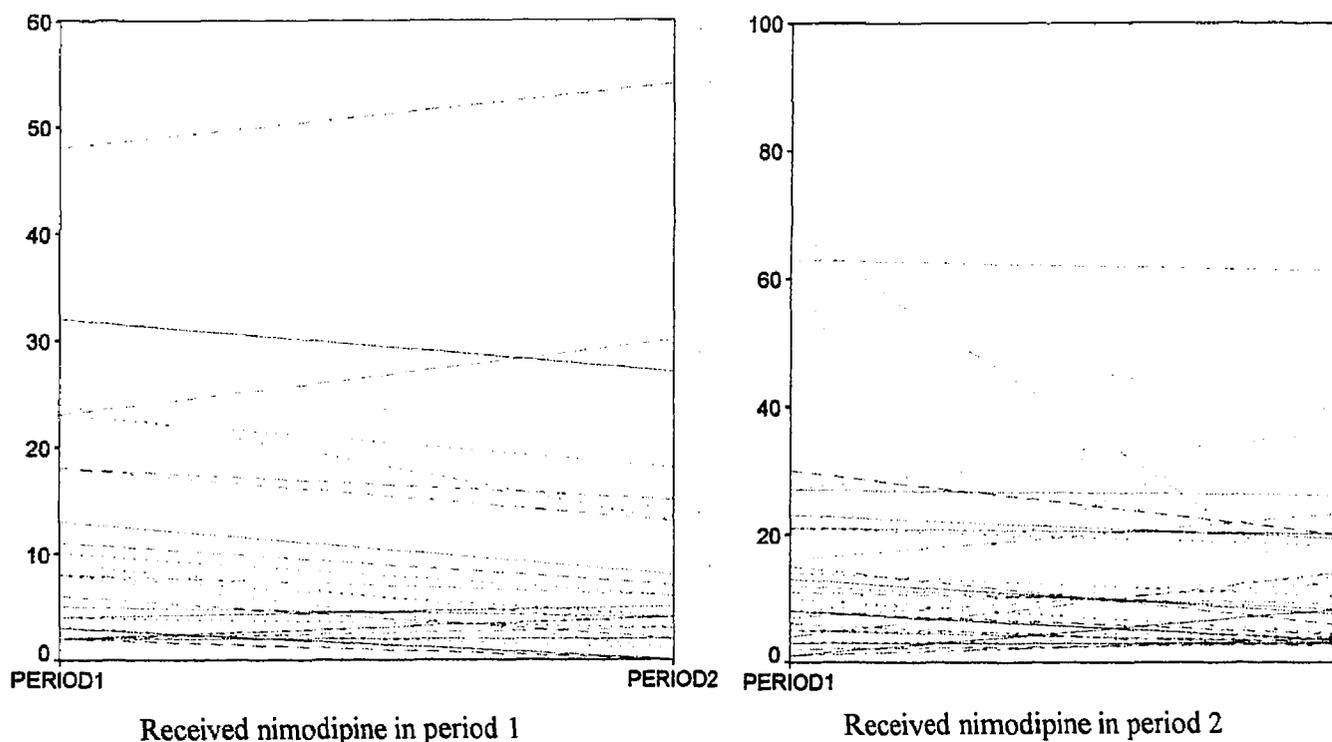
		Run-in period A	Run-in period B	Period 1	Washout period	Period 2
Group 1, received nimodipine during period 1	Mean	16.2	14.9	11.0	13.5	8.4
	N	41	42	41	40	36
	Std. Deviation	13.0	12.0	10.3	12.1	10.7
Group 2, received nimodipine during period 2	Mean	20.2	22.3	17.9	18.9	16.4
	N	40	44	44	43	40
	Std. Deviation	17.0	22.1	19.5	19.1	17.6
Total	Mean	18.2	18.6	14.6	16.3	12.6
	N	81	86	85	83	76
	Std. Deviation	15.1	18.2	16.0	16.3	15.2

Figure 6 - Number of incontinent episodes, mean and 95% confidence intervals, by group and period



Group 1 received nimodipine during period 1, while Group 2 received nimodipine during period 2

Figure 7 - Total number of incontinent episodes, by individual, period 1 and 2, for group 1 (left) and group 2 (right)



The cross procedure is a within subjects comparison of treatment effect, ie, nimodipine versus placebo for each subject, regardless of period in which a specific treatment is received. For all 76 participants who received both nimodipine and placebo, and completed both voiding records, there were an average .03 fewer incontinent episodes with placebo ($t = .019$, $P = .965$ by one sample t-test, 95% CI -2.7 to 2.7 incontinent episodes over the 5 day voiding record - see table 4). As a reduction by even 2.7 incontinent episodes over a 5 day period (the upper limit of the confidence interval) would still represent less than a 15% reduction in incontinent episodes attributable to nimodipine, it is unlikely there is a clinically significant improvement with nimodipine.

The par procedure is a between subjects comparison, nimodipine versus placebo, based only on period 1 data, using runin period B data as a baseline. Based on the 85 subjects for whom both voiding records were available, there were an average .27 fewer incontinent episodes with placebo ($t=.130$, $P=.897$ by paired sample t-test, 95% confidence intervals, 4.00 fewer incontinent episodes with placebo, 3.51 fewer incontinent episodes with nimodipine).

Tests for a first order carryover effect and a second order carryover effect (see section 3.7) were not significant ($t=.774$, $P=.441$, and $t=.144$, $P=.886$, respectively, by independent samples t-test).

A 3-way sensitivity analysis was performed, using the cross procedure, assuming:

- a) all dropouts ($n=10$) had an equal response to nimodipine versus placebo, or
- b) all dropouts were cured of their incontinence by nimodipine, or
- c) all dropouts were cured of their incontinence by placebo.

For assumption a), mean number of incontinent episodes was .02 less with placebo, $t=.019$, $P=.985$, 95% confidence intervals 2.0 fewer incontinent episodes with nimodipine, 2.0 fewer incontinent episodes with placebo. For assumption b), mean number of incontinent episodes was 1.72 less with nimodipine, $t=1.303$, $P=.196$, 95% confidence intervals 4.1 fewer incontinent episodes with nimodipine, .9 fewer incontinent episodes with placebo. For assumption c), mean number of incontinent episodes was 1.76 less with placebo, $t=1.339$, $P=.184$, 95% confidence intervals 4.2 fewer incontinent episodes with placebo, .8 fewer incontinent episodes with nimodipine. The lack of significance with the above analyses would suggest the results are fairly robust. For subsequent analyses of the voiding records, the within subject differences, period 1 versus period 2 were used, ie, the cross procedure.

There were no significant differences noted, placebo versus nimodipine, in daytime or nocturnal urinary frequency, or in daytime or nocturnal incontinent episodes (see Table 4)

Table 4 - Daytime and Nocturnal Voiding and Incontinent Episodes, Nimodipine versus Placebo.

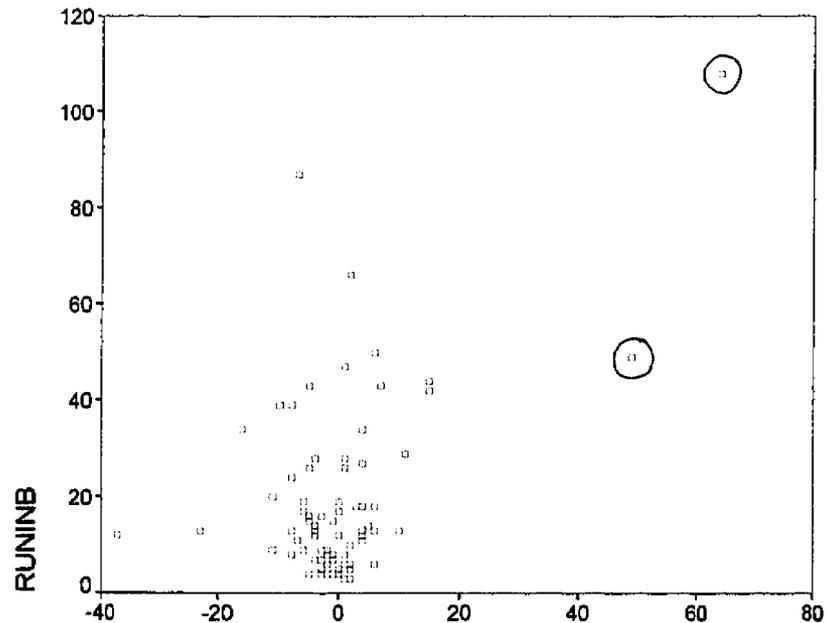
	Difference in # of events, nimodipine versus placebo*	Standard Deviation	t	p	95% confidence interval of the difference
Daytime voiding episodes	.013	8.61	.013	.989	-1.96, 1.99
Daytime incontinent episodes	-.280	10.09	.240	.811	-2.60, 2.04
Nocturnal voiding episodes	-.253	4.08	.537	.593	-1.19,.69
Nocturnal incontinent episodes	-.160	3.04	.456	.649	-.86,.54
Total voiding episodes	-.118	10.42	.099	.921	-2.49,2.26
Total incontinent episodes	-.03	11.97	.019	.985	-2.76,2.71

N = 75 or 76 for the above table; one subject failed to separate episodes of urination and incontinence into daytime versus nocturnal.

* - Negative values indicate fewer events with placebo, positive values indicate fewer events with nimodipine.

An initial linear regression analysis also suggested that a greater number of incontinent episodes in run-in period B (ie, more severe incontinence at baseline) was associated with a greater reduction in incontinent episodes in response to nimodipine ($R=.478$, $t=4.676$, $P<.001$); however, with the exclusion of two outliers (see figure 7; outliers which were excluded are circled), a repeat linear regression analysis revealed no significant association ($R=.097$, $t=.825$, $P=.412$).

Figure 8 - Number of incontinent episodes with placebo minus number of incontinent episodes with nimodipine, versus number of incontinent episodes during run-in period B, by individual



Number of incontinent episodes during run-in B is on the Y axis, number of incontinent episodes (nimodipine minus placebo) is on the X axis (positive numbers represent fewer incontinent episodes with nimodipine)

4.3 Incontinence Impact Questionnaire (IIQ)

The IIQ was analyzed in two parts: questions 1 through 17 (hence referred to as IIQ17), which were answered twice in the run-in period, then at the end of period 1, the washout period, and period 2; questions 18, 19, and 20 which were answered at the end of periods 1,2, and the washout period only. IIQ questions 18,19, and 20 asked participants to rate, for the previous week, how the number of incontinent episodes compares to before receiving treatment, how the amount of urine leaked compares to pretreatment, and how the urgency to urinate compares to pretreatment, respectively.

The test-retest reliability for the IIQ17 summary score was .807 (Pearson correlation coefficient) for the 96 participants who completed the IIQ17 during both run-in period A and run-

in period B, and was .816 for the 86 participants who were randomized, with a Cronbach's alpha for these 17 items of .918 and .916, respectively. There were no significant differences in correlation for the IIQ17 between subjects who were randomized and those who were not. The average intra-individual difference in IIQ17 summary scores, run-in period A versus run-in period B, was 6.76 (total score is out of 85), with a standard error of .63.

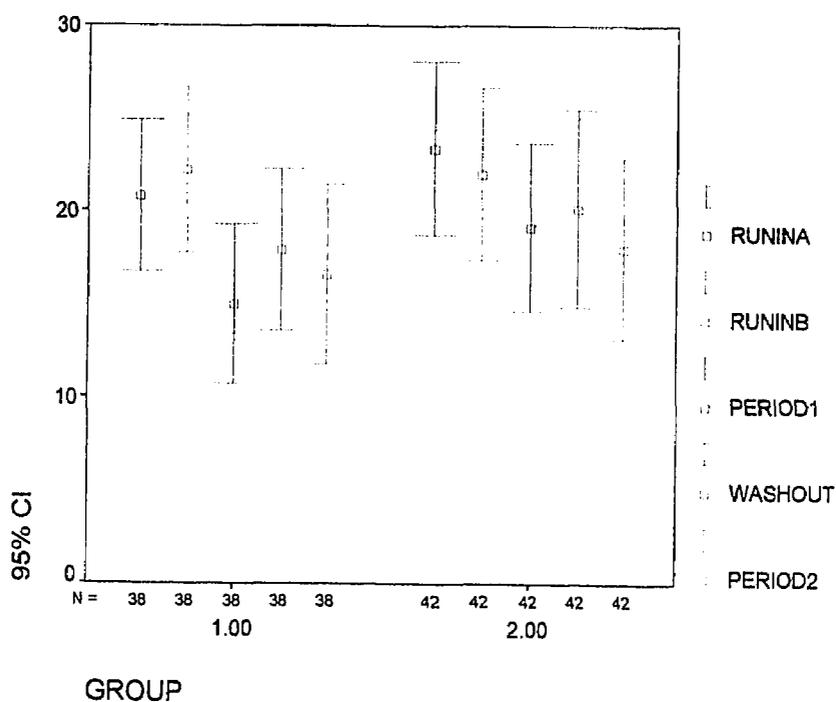
IIQ17 summary scores by period are shown in Table 5, and graphically in figure 9. IIQ17 summary scores decreased over time, independent of treatment, suggestive for a period effect ($F=12.516$, $P<.001$ by GLM repeated measures, $F=1.307$, $P=.267$ for the addition of Group 1 versus Group 2 as a between subjects factor, suggesting that this change over time was independent of treatment given). Within subjects comparison of IIQ17 summary scores in period 1 and period 2 (cross procedure) revealed a 1.36 point lower score with nimodipine versus placebo ($t=1.85$, $P=.068$). Between subjects comparison of IIQ17 summary scores in period 1 (par procedure) revealed a 4.13 point lower score with nimodipine versus placebo in period 1 ($t=2.431$, $P=.017$ by independent samples t-test). Although statistically significant, this 4.13 change on the IIQ17 summary score is unlikely to be of clinical significance. The average intra-individual difference noted during the run-in periods was 6.76 points, while a 10 point decline was noted with a similar version of the IIQ in response to behavioural therapy in another study.⁹

Tests for a first order carryover effect and a second order carryover effect (see section 3.7) were not significant ($t= 1.576$, $P=.119$, and $t= 1.334$, $P=.188$, respectively, by independent samples t-test).

Table 5 - IIQ17 summary scores, by group and period

		Run-in period A	Run-in period B	Period 1	Washout period	Period 2
Group 1, received nimodipine during period 1	Mean	20.23	21.88	14.97	18.46	16.60
	N	42	42	41	39	38
	Std. Deviation	12.80	13.90	13.13	13.49	14.72
Group 2, received nimodipine during period 2	Mean	23.70	22.38	19.27	21.00	18.00
	N	44	44	44	43	42
	Std. Deviation	15.23	15.10	14.38	17.71	15.58
Total	Mean	22.01	22.14	17.20	19.79	17.34
	N	86	86	85	82	80
	Std. Deviation	14.13	14.45	13.88	15.80	15.10

Figure 9 IIQ17 summary score, mean and 95% confidence interval, by group and period



Group 1 received nimodipine during period 1, while Group 2 received nimodipine during period 2

A linear regression analysis was undertaken to see if there was an association between IIQ17 score at baseline (run-in period B) and greater reduction in IIQ17 summary score with nimodipine than placebo. The resulting model ($R=.085$, $t=.756$) was not significant ($P=.452$).

Participant's answers to IIQ questions 18, 19, and 20 did not differ significantly while on nimodipine versus placebo ($P=.698$, $.777$, and $.607$, respectively).

4.4 American Urologic Association Symptom Scores (AS)

The test-retest reliability for the AS (sum of seven questions) was $.790$ (Pearson correlation coefficient), for the 96 participants who completed the AS during both run-in period A and run-in period B, and $.786$ for the 86 participants who were randomized, with Cronbach's alpha for these 7 items of $.762$, and $.766$, respectively. Test retest reliability on the quality of life question added to the AS (96 subjects completed both, 86 were randomized) was $.838$ for both groups. There were no significant differences in correlation, for the AS or quality of life question, between subjects who were randomized versus those who were not.

AS scores by period are shown in Table 6, and graphically in figure 10. AS scores decreased over time, independent of treatment, suggestive for a period effect ($F=13.96$, $P<.001$ by GLM repeated measures, $F=.817$, $P=.515$ for the addition of Group 1 versus Group 2 as a between subjects factor, suggesting that this change over time was independent of treatment given). Within subjects comparison of AS scores in period 1 and period 2 revealed a 0.63 (out of 35) point lower score with nimodipine versus placebo ($t=1.25$, $P=.215$). Between subjects comparison of AS scores in period 1 revealed a 1.36 point lower score with nimodipine versus placebo ($t=1.316$, $P=.192$). This is unlikely to represent a clinically significant difference, given

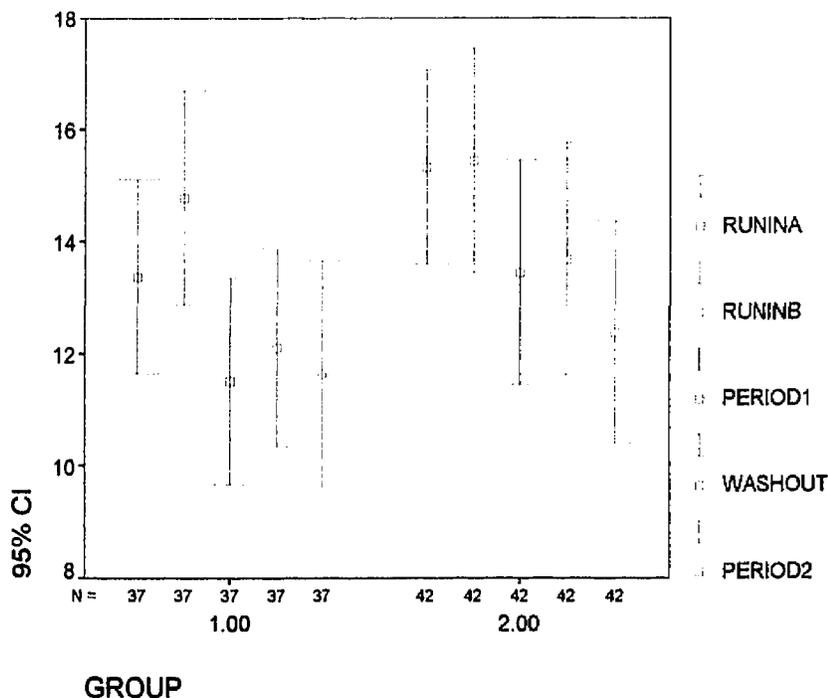
that the average intraindividual difference in AS scores during the run-in period was 3.24 (SD =2.50), and that the average change in AS score noted in a recent trial of combined behavioural and drug therapy for women with UI was 8.2.⁵⁸

Tests for a first order carryover effect and a second order carryover effect (see section 3.7) were not significant ($t = .871$, $P = .386$, and $t = .057$, $P = .954$, respectively, by independent samples t-test).

Table 6 - AS scores, by group and period

	run-in period A	run-in period B	period 1	washout period	period 2
Group 1 - received nimodipine in period 1					
Mean	13.28	14.19	11.39	12.36	11.65
N	42	42	41	39	37
Standard Deviation	5.90	5.98	5.74	5.53	6.04
Group 2 - received nimodipine in period 2					
Mean	14.86	14.98	13.30	13.56	12.38
N	44	44	44	43	42
Standard Deviation	5.87	6.65	6.36	6.63	6.39
Total					
Mean	14.09	14.59	12.38	12.99	12.04
N	86	86	85	82	79
Standard Deviation	5.91	6.30	6.11	6.12	6.20

Figure 10 - AS score, mean and 95% confidence interval, by group and period



Group 1 received nimodipine during period 1, while Group 2 received nimodipine during period 2

There was no significant difference in the score on the quality of life question added to the AS, nimodipine versus placebo (.1 out of 6 improvement with nimodipine, $t=.591$, $P=.556$)

4.5 Effect of age and sex upon the 3 major outcome measures

There was a correlation between participant age and baseline severity of incontinence; older participants had a higher number of incontinent episodes at baseline ($R=.308$, $P<.01$), and had a higher AS score at baseline ($R=.249$, $P<.05$). There was no significant correlation between age and baseline IIQ17 score ($R=.063$, $P=.547$). There was no significant effect of age upon likelihood of response to nimodipine; linear regression analysis of age versus change in total number of incontinent episodes with nimodipine versus placebo was not significant ($R = .104$, F

= .814, $P = .370$).

There was no significant correlation between sex of participant and baseline severity of incontinence, as measured by number of incontinent episodes, IIQ17 score, or AUASS score, singly or combined in a logistic regression analysis (data not shown). There was a significant effect of sex upon likelihood of response to nimodipine, however, in that males ($n=12$) had a significantly greater response to placebo than nimodipine, while females ($n=64$) had a greater response to nimodipine than placebo (males had 6.75 more episodes of incontinence with nimodipine, SD 10.61, females had 1.23 more episodes of incontinence with placebo, SD 11.90, $T = 2.17$, $P = .032$). This change in number of incontinent episodes, nimodipine versus placebo for the 64 female study participants was not significant when analyzed separately, however (1.23, SD 11.90, $t = .823$, $P = .408$, 95% confidence intervals 1.7 fewer incontinent episodes with placebo, 4.1 fewer incontinent episodes with nimodipine). There were no significant differences, male versus female, in response to nimodipine versus placebo as measured by change in IIQ17 score (.33 higher in males, versus 1.66 lower in females with nimodipine, $t = .967$, $P = .336$). When analyzed as a subgroup, the 1.66 point decline in IIQ17 score for the 68 female study participants with nimodipine versus placebo was statistically significant ($t = 2.023$, $P = .04$); this is unlikely to represent a clinically significant change, given that the average intra-individual difference noted during the run-in periods was 6.76 points, while a 10 point decline was noted with a similar version of the IIQ in response to behavioural therapy in another study.⁹ The change in AS score with nimodipine versus placebo was not significantly different for males versus females (-1.00 versus -.567, $t = .305$, $P = .761$).

4.6 Adverse effects

Adverse Effects Questionnaire

All 86 subjects who were randomized were asked to complete a 18 item adverse effects questionnaire, at the end of the nimodipine and placebo treatment periods. The results are shown in the following table. Each question was scored as a 5 point Likert scale from much more than usual (1) to much less than usual (5). The mean difference in scores while on nimodipine versus placebo is shown in column 5, and was calculated by subtracting the score while on placebo from the score while on nimodipine. No statistically significant differences were noted; although not statistically significant, the increased frequency of lightheadedness, fatigue, confusion, and chest pain or heartburn noted with nimodipine versus placebo may be clinically significant, especially in light of recent studies suggesting increased cardiac toxicity with calcium channel blocking medications (see discussion).

Table 7 - Responses to adverse effects questionnaire

Question	number of participants reporting more symptoms with nimodipine	number of participants reporting more symptoms with placebo	# of paired responses	mean difference	t	p
Dizziness	9	9	80	-.01	.19	.849
Lightheadedness	15	8	79	-.07	1.09	.276
Fatigue	30	21	79	-.07	.69	.495
Nausea or vomiting	5	7	79	.00	.00	1.00
Diarrhea	8	7	79	-.01	.20	.843
Abdominal Pain	6	6	79	.1	.36	.717
Constipation	6	12	79	.00	1.47	.145
Drowsiness	20	18	78	-.09	.00	1.00
Insomnia	9	6	77	.04	1.22	.265
Headache	8	9	77	-.05	.46	.650
Confusion	6	3	78	.04	.94	.349
Rash or itchy skin	9	9	79	.06	.58	.567
Changes in your vision	9	8	78	-.01	1.15	.354
Joint pain or swelling	16	16	78	-.01	.16	.881
Muscle pain or cramps	17	20	78	.06	.74	.460
Pain on urination	2	1	77	.00	.00	1.00
Chest pain or heartburn	11	5	78	-.06	1.40	.167
Palpitations	2	2	78	-.01	.38	.708

Post-void residuals

Post-void residual urine volumes were measured for 79 participants at the end of period 1 and period 2. There were no complications, such as bleeding or infection associated with

catheterization. Mean residual urine volume was 29.1 mls (23.7 for males, 30.1 for females, $P=.370$). The difference in residual urine volume, nimodipine versus placebo, was .8 ml (higher with placebo, $t=.249$, $P=.804$) which is not clinically significant. A post-void residual urine volume greater than 100 mls is a clinical indication of inadequate bladder emptying¹¹; this occurred in 4 participants with nimodipine, in 3 participants with placebo, and in all cases the post-void residual urine volume was less than 150 mls. By comparison, normal bladder capacity is usually greater than 350 mls.¹¹

Blood Pressure

Systolic and diastolic blood pressures, lying and standing, were measured in all participants during the run-in period, and at the end of period 1 and period 2. A statistically significant decrease in systolic blood pressure was noted with nimodipine versus placebo (3.55 mm Hg, $t=2.20$, $P=.03$), and a borderline statistically significant decrease in diastolic blood pressure was noted with nimodipine versus placebo (1.56 mm Hg, $t=1.81$, $P=.074$). A 20 point drop in systolic blood pressure, and/or a 10 point drop in diastolic blood pressure are common measures of a clinically significant orthostatic hypotension⁷⁵; a change of this magnitude occurred in 5 participants while receiving nimodipine, and in 6 participants while receiving placebo.

4.7 Compliance

Pill counts were performed at the end of periods 1 and 2. Pill counts would indicate that participants took 95% of the study drug (39.9/42 pills) while on nimodipine, and 96% of the study drug (40.3/42 pills) while on placebo (difference =.38 pills, $t=.454$, $P=.651$). This would suggest

that compliance with the intervention was excellent, and did not differ significantly while on nimodipine versus placebo.

4.8 Maintenance of Double-Blinding

At the ends of periods 1 and 2, all participants and the research assistant were asked if they could guess whether they had just received nimodipine or placebo, as a method of determining whether blinding was maintained. A total of 166 responses were received from the research assistant and participants (response rate 94%).

The research assistant correctly identified treatment as nimodipine or placebo in 50 of 96 cases (52%), and was unsure on 70 occasions. The participants correctly identified treatment as nimodipine or placebo in 63 of 108 cases (58%), and were unsure on 58 occasions. In neither case was identification of treatment correct beyond that predicted by chance ($p = .844$ and $.171$, respectively by chi-square). This would suggest that double blinding was not lost during the study.

5 Discussion

5.1 Methodologic Issues Regarding Data Analysis in Crossover Trials

The implications of using the Grizzle test to assess for a carryover effect have been described by Brown, Senn, Freeman, and others.⁷⁰⁻⁷² The likelihood that a significant carryover effect, if present, will be missed by the Grizzle test is quite high; Senn and Freeman discuss typical cases wherein the probability of type I and II errors using the Grizzle test to determine whether a carryover effect is present or not are 40 and 68%, respectively.^{71,72} In recognition of this, Freeman and Brown, respectively, have recommended a) the avoidance of crossover trials altogether, unless the possibility of a carryover effect can be ruled out a priori; or b) the use of sample sizes LARGER than required for a comparable parallel-groups design, in order to detect a carryover effect with similar statistical power ($\alpha = .05$). The clinical reality, unfortunately, is that the possibility of a carryover effect can never be ruled out, a priori, and that crossover trial design is usually employed to maximize power to detect a significant difference with a given, and often limited, sample size.

Willan, and Willan and Pater, have suggested an alternative method for analyzing data from crossover trials.^{68,74} They started by developing a formula to determine how big a carryover effect must be to make analysis as a parallel design study preferable, ie., using first period data only. Willan operationalized this formula in a subsequent publication; he proposes the simultaneous use of crossover and parallel analysis, with choosing of the analysis that gives the larger corresponding test statistic as the 'best fit'.⁶⁸ The major assumption in this model is that a carryover effect cannot occur in the absence of a treatment effect. In this trial, analysis of the primary outcome measure by the Willan test suggests there is no treatment effect. Not

surprisingly, very similar results were obtained with analysis using the cross procedure alone (data not shown). The simulation that was undertaken suggests that the Willan test is the most sensitive for detecting a treatment effect in the absence of a carryover effect, given several assumptions; the data obtained in this trial, most importantly the intrasubject correlation coefficients for the VR, AS, and IIQ17, was consistent with these assumptions.

The difficulty lies in determining whether or not there may have been a carryover effect, ie, that the difference between treatment and placebo may have been influenced by the period in which each was given. Kenward and Jones developed a model for 2X2 crossover trials that incorporates baseline measurements, and divides the carryover effect into first order (present at the washout between period 1 and period 2) and second order (present at the end of period 2) carryover effects.⁷³ Evaluation of this model with several data sets suggested that the power to detect a treatment difference in the presence of a carryover effect can be increased by using the additional information provided by baseline measurements (if the additional variance isn't too large), but remains less than the power to detect a treatment difference in the absence of a carryover effect. Jones and Lewis, in an extensive subsequent publication, compared several proposed models for dealing with carryover effects in crossover trials; in their discussion they suggest a) that loss of power is inevitable, and varies with increasing size of carryover effect in crossover trials, and b) that inclusion of baseline measurements results in little, if any, gain in power.⁶⁰ In both papers, it was assumed that a carryover effect can only occur in the presence of a treatment effect, and that only positive carryover effects can occur, ie that a treatment in period 1 can enhance, but not prevent a response to treatment in period 2. In both papers, as with the Grizzle test, between subjects comparisons are used to determine whether a carryover effect is

present.

The paradigms of analyzing a crossover trial, therefore would seem to be that in the presence of a carryover effect, randomization does not result in the treatment groups being equal, and that only low power testing is available to determine whether a carryover effect exists. The tests for first or second order carryover effects carried out here did not support the presence of carryover effects for any of the three major outcome measures (VR, AS, or IIQ17). It is still possible that a carryover effect may have been present; if present, a carryover effect would have decreased the power available to detect a treatment effect, and hence increased the chance of a type II error. If there were no treatment effect AND a negative carryover effect, then a larger difference between treatment and placebo should have been seen in the second period than the first; this did not occur. The consistency of the results, specifically the general lack of a significant difference with any of the three major outcome measures, using a variety of analytic techniques, suggests that these are all unlikely.

Interestingly, if our study had been done as a simple, parallel randomized trial without baseline measures, we may have concluded (based on period 1 results) that nimodipine was an effective treatment for UI, as it reduced the number of incontinent episodes by almost 40% (17.9 to 11.0 incontinent episodes, $t=2.044$, $P=.04$), and IIQ17 score by over 4 points (19.27 to 14.97, $t=1.43$, $P=.155$) (see tables 3 and 5).

5.2 General

Nimodipine did not result in a significant reduction in incontinent episodes in this trial. The 95% confidence intervals using the cross procedure rule out even a 15% reduction in incontinent episodes with nimodipine, while the 95% confidence intervals using the par procedure (first period data only) rule out even a 20% reduction in incontinent episodes with nimodipine. As there cannot be a carryover effect when analysis is restricted to first period data, and the results are very similar with the par and cross procedures, it is unlikely that these results are confounded by a significant carryover effect.

There were differences approaching statistical significance in the total number of incontinent episodes between Group 1 (who received nimodipine in period 1) and Group 2 (who received nimodipine in period 2) in run-in period B, ie, before any intervention ($t=1.932$, $P = .058$ by independent sample t-test) (see table 2). When voiding records for run-in period A and B were pooled, however, the differences between group 1 and group 2 were smaller ($t=1.414$, $P= .139$). These differences persisted throughout the study, however, and were significant in period 2 (8.4 episodes in group 1, 16.4 episodes in group 2, $t=2.36$, $P=.021$ by independent samples t-test). Unlike the voiding records, subjects randomized to receive nimodipine in period 1 versus period 2 did not differ significantly in IIQ17 summary score or AS score in run-in period B (data not shown). For all three outcome measures, regression analysis looking for an association between incontinence severity and likelihood of response to nimodipine versus placebo was not significant. Severity of incontinence is a potential confounding variable in therapeutic trials for UI. In this trial, stratification for severity of urinary incontinence was considered, but did not occur due to uncertainty regarding appropriate cutoff values for severity of incontinence. In future trials,

severity of incontinence should be controlled for with stratification, if possible.

Two statistically significant changes were noted with the modified version of the IIQ used in this trial: a 4.13 point difference with nimodipine versus placebo in period 1, and a 4.80 point difference from run-in B to period 2 independent of treatment. These changes, although not clinically significant, would suggest that the version of the IIQ used here has at least modest responsiveness. The test-retest reliability for the IIQ17 summary score of .816 in our study compares favorably with the previously reported test-retest reliability of .73 in a younger, healthier population with both stress and urge incontinence.⁵⁵ The version of the IIQ used here may be sufficiently reliable and responsive for use in future therapeutic trials for geriatric UI, although further studies are needed to confirm this.

Statistically significant changes in AS score were also noted from run-in B to period 2 independent of treatment, consistent with at least moderate responsiveness. In this study, the AS had lower test-retest reliability (.786) than previous studies of elderly men with benign prostatic hypertrophy (.93) and postmenopausal women with predominantly stress incontinence (.84)^{57,58}; it is likely that it is still sufficiently reliable for use in future geriatric UI trials, although further trials are necessary to confirm its validity and usefulness in UI, especially in female patients.

The clinical significance of the statistically significant association between increasing age and more severe incontinence at baseline, as measured by the VR and AS, is unclear. It is possible that a referral bias occurred, such that, amongst the 'old-old', only those with more severe incontinence were willing, or able, to participate in a trial such as ours. Alternatively, UI severity may actually increase with age; this has not been addressed in previous studies, to my knowledge, although the increasing prevalence of urinary incontinence of all types with increasing

age is well documented.¹¹ Further examination of the comorbidity data collected for each of the participants in this study may shed further light upon the association noted between participant age and incontinence severity.

The gender difference in patterns of response to nimodipine versus placebo is interesting. By both the VR and the IIQ, male participants tended to get worse with nimodipine, while female participants tended to get better with nimodipine. The etiology of geriatric UI is diverse, and poorly understood; it is possible that there are gender differences in the disease itself, or in response to medications such as nimodipine. Previous studies of nimodipine have not commented on gender differences in response to nimodipine.³⁸⁻⁵⁰ Previous therapeutic trials for UI have mainly involved women; a meta-analysis to determine whether there is a significant sex-related difference in response to pharmacologic agents for UI in general, or for specific classes of agents for UI, has not been done. Until there is a greater understanding of gender differences in the etiology of geriatric UI, or in responses to treatments, therapeutic trials should either stratify by gender, or be limited to one sex or the other. The major risk for trials that do not make such allowances is that they may lack sufficient power to determine whether there is a treatment effect (type II error).

With regards to adverse effects, the absence of any significant change in post-void residual urine volume, or in answers to the adverse effects questionnaire, is reassuring. The statistically significant drop in systolic blood pressure noted with nimodipine (3.55 mm Hg) was unexpected, given that previous studies have found no change in blood pressure with similar doses of nimodipine in elderly patients.⁴³ Large declines in blood pressure occurred in only 5 participants while receiving nimodipine, and in 6 participants while receiving placebo, while no significant

difference was noted in likelihood of orthostatic hypotension. Careful evaluation of blood pressure should continue to be included as part of the assessment of elderly participants in any future trials of nimodipine.

Compliance with the study medication was assessed only via pill count in this trial. Measuring serum levels of nimodipine is possible, and would be a more definitive measure of compliance. Pill counts suggested that compliance was very similar with placebo and nimodipine, which would suggest that blinding was maintained. The inability of either the research assistant or the study participants to identify the treatment received beyond that predicted by chance provides even more support that double-blinding was maintained throughout the study. In previous RCTs of drugs for UI (particularly anticholinergic medications, which frequently cause dry mouth), participants have often been quite successful at identifying treatment as active drug or placebo.³²

The three major outcome measures used in this trial (VR, IIQ17, and AS) have rarely, if ever been collected on the same participants. They represent three important constructs, specifically the number of incontinent episodes (VR), more general urinary symptoms (AS), and the impact of incontinence and urinary symptoms upon psychosocial function (IIQ17). The test-retest reliability for each measure used in this study was .78 or greater, and each measure demonstrated at least modest responsiveness, suggesting that it is feasible to use any or all of these measures in future studies involving elderly participants. The modest correlation between these three measures would support the supposition that they are measuring different phenomena. The lack of change with these measures may reflect a lack of sensitivity. However, there are several studies involving each of the measures in which significant changes with therapy have been documented. As the version of the IIQ used here appears to be similarly reliable when compared

to previous versions (test-retest reliability over .8 in our study versus .73 in Wyman et al's study)⁵⁵, it needs to be tested with clearly effective medications, and behavioural therapies to confirm responsiveness, or lack thereof. Comparison to other, more recently developed questionnaires in this area would also be useful. Yu et al, have developed a questionnaire assessing the psychosocial impact of urinary incontinence in elderly women residing in nursing homes, which unfortunately suffers from poor test-retest reliability; on the other hand, Lee et al, have recently published another scale that has been shown to be reliable and responsive to therapy for UI in community dwelling postmenopausal women, and hence could serve as a 'gold standard' for further assessment of the IIQ.^{78,79}

There are concerns regarding the class-related toxicity of short-acting calcium channel blockers like nimodipine. There are several recent cohort studies suggesting that short-acting calcium channel blockers may increase cardiovascular mortality, gastrointestinal hemorrhage, myocardial infarction and cancer risk in elderly persons taking calcium channel blockers, as opposed to other antihypertensive medications.^{75,76,80,81} The cohort studies mentioned refer to the use of short-acting calcium channel blockers for the treatment of hypertension, and predominantly refer to nifedipine, a very potent antihypertensive. It remains unclear if the adverse effects attributed to short-acting calcium channel blockers in these studies can be extended to include nimodipine. On the other hand, terodiline is a short-acting calcium channel blocker which, like nimodipine, has minimal effect upon blood pressure. Terodiline has been shown to be effective for UI, but has recently been removed from the market in Europe, and trials in the United States have been discontinued because of an association with ventricular arrhythmias.¹¹

There has also been a recent RCT of nimodipine versus placebo to reduce postoperative

neurologic deficit in patients undergoing cardiac valve replacement; this study was terminated early because of increased mortality in the nimodipine patients, while no significant difference was noted in the incidence of neurologic deficits.⁸² There are two major concerns regarding the generalizability of this study. Most of the excess mortality due to nimodipine was attributable to excessive post-operative bleeding, which is perhaps not surprising given that all calcium channel blockers inhibit platelet aggregation and hence coagulation.⁸³ The group randomized to receive nimodipine were also significantly more likely to have congestive heart failure and pulmonary disease pre-operatively, both of which are strong predictors of poorer outcomes post-operatively.⁸⁴

The sample size in this trial is too small to adequately determine whether clinically important cardiovascular toxicity occurred with nimodipine. Given the recent literature, any further studies of nimodipine would require large sample sizes, and close monitoring for cardiac side effects to rule out clinically important cardiovascular toxicity.

In light of these recent studies suggestive for calcium-channel blocker class-related toxicities, and the lack of efficacy noted with nimodipine for UI in this trial, it would seem prudent to discourage further use or research involving nimodipine, and perhaps calcium-channel blockers in general for the treatment of UI.

6 Conclusions

Based upon the lack of a significant improvement in voiding records, urinary symptom scores, and quality of life measures, nimodipine is ineffective for the treatment of geriatric urge incontinence. Although nimodipine appears to have been well-tolerated, its lack of efficacy and possible class-related toxicity are both important reasons to discourage further use of this drug to treat urge incontinence. Further work is needed to determine optimal outcome measures to demonstrate the effectiveness of therapies for urge incontinence.

References

1. Herzog et al, Methods Used to Manage Urinary Incontinence by Older Adults in the Community, *Journal of the American Geriatrics Society*, 1989; 37:339-344.
2. Resnick NM, Yalla SV and Laurino E, The Pathophysiology of Urinary Incontinence Among Institutionalized Elderly Persons, *New England Journal of Medicine*, 1989; 320(1):1-7.
3. Ouslander JG, Urinary Incontinence in the Elderly, *Western Journal of Medicine*, 1981; 135:482-486.
4. Hu TW, Impact of Urinary Incontinence on Health-Care Costs, *Journal of the American Geriatrics Society*, 1990; 38:292-295.
5. Resnick NM, Voiding Dysfunction and Urinary Incontinence, in *Geriatric Medicine*, second edition, Cassel et al (eds), 1990.
6. McGuire EJ and Savastano JA, Stress Incontinence and Detrusor Instability/Urge Incontinence, *Neurourol Urodynam*, 1985: 4:313-316.
7. Abrams P, Detrusor Instability and Bladder Outlet Obstruction, *Neurourol Urodynam*, 1985; 4:317-328.
8. Burton JR, Pearce KL, Burgio KL, et al, Behavioural Training for Urinary Incontinence in Elderly Ambulatory Patients, *Journal of the American Geriatric Society*, 1988; 36:693-698.
9. Fantl JA, Wyman JF, McClish, DK, et al, Efficacy of Bladder Training in Older Women with Urinary Incontinence, *JAMA*, 1991; 265:609-613.
10. Ouslander JG, Blaustein J, Connor A, Pitt A, Habit Training and Oxybutynin for Incontinence in Nursing Home Patients: A Placebo-controlled Trial, *Journal of the American Geriatrics Society*, 1988; 36:40-46.
11. Urinary Incontinence in Adults: Acute and Chronic Management: Clinical Practice Guideline Number 2, 1996 Update (AHCPR Publication No. 96-0682), Rockville MD: Agency for Health Care Policy and Research, 1996.
12. Schnelle JF, Treatment of Urinary Incontinence in Nursing Home Patients by Prompted Voiding, *Journal of the American Geriatrics Society*, 1990; 38:356-360.
13. Castleden CM, Duffin HM, and Gulati RS, Double-blind Study of Imipramine and Placebo for Incontinence due to Bladder Instability, Age and Aging, 1986; 15:299-303.

14. Whitehead JA, Urinary Incontinence in the Aged. Propantheline Bromide as an Adjunct to Treatment, *Geriatrics*, 1967; 22:154-158.
15. Beck RP, Arnusch D, and King C, Results in Treating 210 Patients with Detrusor Overactivity in Incontinence of Urine, *American Journal of Obstetrics and Gynecology*, 1976; 125:593-596.
16. Thuroff JW, Bunke B, Ebner A, et al, Randomized Double-blind Multicentre Trial on Treatment of Frequency, Urgency and Incontinence Related to Detrusor Hyperactivity: Oxybutynin Versus Propantheline Versus Placebo, *Journal of Urology*, 1991; 145:813-815.
17. Zorzitto ML, Jewett MAS, Fernie GR, et al, Effectiveness of Propantheline Bromide in the Treatment of Geriatric Patients with Detrusor Instability, *Neurourology and Urodynamics*, 1986; 5:133:140.
18. Holmes DM, Montz FJ, and Stanton SL, Oxybutynin Versus Propantheline in the Management of Detrusor Instability: A Patient-regulated Variable Dose Trial, *British Journal of Obstetrics and Gynecology*, 1989; 96:607-612.
19. Lose G, Jorgensen L, and Thunedborg P, Doxepin in the Treatment of Female Detrusor Overactivity: A Randomized Double-blind Crossover Trial, *Journal of Urology*, 1989; 142:1024-1026.
20. Milner G, and Hills NF, A Double-blind Assessment of Antidepressants in the Treatment of 212 Enuretic Patients, *Medical Journal of Australia*, 1968; 1:943-947.
21. Palmer JH, Worth PHL, Exton-Smith AN, Flunarizine: A Once-daily Therapy for Urinary Incontinence, *Lancet*, 1981; 296:279-281.
22. Palmer JH, Worth PHL, and Exton-Smith AN, Flunarizine: Short-term Fact, Long-term Fantasy? *Proceedings of the British Foundation for Age Research*, 1982.
23. Gerstenberg TC, Klarskov R, Ramirez D and Hald T, Terodiline in the Treatment of Women with Urgency and Motor Urge Incontinence: A Clinical and Urodynamic Double-blind Cross-over Study, *British Journal of Urology*, 1986; 58:129-133.
24. Klarskov P, Gerstenberg TC, and Hald T, Bladder Training and Terodiline in Females with Idiopathic Urge Incontinence and Stable Detrusor Function, *Scandinavian Journal of Urology and Nephrology*, 1986; 20:41-46.
25. Lukkarinen, O, Grohn P, Wilen-Rosenqvist G, et al, A Controlled, Double-blind, Cross-over Study of Terodiline in Motor Urge Incontinence, *Annales Chirurgiae et Gynaecologiae*, 1987; 76:128-132.

26. Peters D, Terodiline in the Treatment of Urinary Frequency and Motor Urge Incontinence. A Controlled Multicentre Trial, *Scandinavian Journal of Urology and Nephrology*, 1984; 87:21-33.
27. Petersen T, and Jakobsen J, A Calcium Blocking and Anticholinergic Agent (Terodiline) in the Treatment of Detrusor Hyperreflexia: A placebo-controlled, Cross-over Trial, *Journal of Neurology, Neurosurgery and Psychiatry*, 1987; 50:1331-1336.
28. Tapp A, Fall M, Norgaard J, et al, Terodiline: A Dose Titrated, Multicentre Study of the Treatment of Idiopathic Detrusor Instability in Women, *Journal of Urology*, 1989; 142:1027-1031.
29. Ulmsten U, Ekman G, and Andersson KE, Effect of Terodiline Treatment in Women with Motor Urge Incontinence, *American journal of Obstetrics and Gynecology*, 1985; 153:619-622.
30. Zorzitto ML, Holliday PJ, Jewett MA, et al, Oxybutynin Chloride for Geriatric Urinary Dysfunction: A Double-blind Placebo-controlled Study, *Age and Aging*, 1989; 18:195-200.
31. Zeegers AGM, Kiesswetter H, Kramer AEJL, and Jonas U, Conservative Therapy of Frequency, Urgency and Urge Incontinence: A Double-blind Clinical Trial of Flavoxate Hydrochloride, Oxybutynin Chloride, Emepronium Bromide and Placebo, *World Journal of Urology*, 1989; 5:57-61.
32. Tapp AJ, Cardozo LD, Versi E, and Cooper D, The Treatment of Detrusor Instability in Post-Menopausal Women with Oxybutynin Chloride: A Double-blind Placebo-controlled Study, *British Journal of Obstetrics and Gynecology*, 1990; 97:521-526.
33. Riva D, and Casolati E, Oxybutynin Chloride in the Treatment of Female Idiopathic Bladder Instability: Results from Double-blind Treatment, *Clinical and Experimental Obstetrics and Gynecology*, 1984; 11:37-42.
34. Moore KH, Hay DM, Imrie AE, et al, Oxybutynin Hydrochloride (3 mg) in the Treatment of Women with Idiopathic Detrusor Instability, *British Journal of Urology*, 1990; 66:479-485.
35. Castleden CM, Duffin HM, and Millar AW, Dicyclomine Hydrochloride in Detrusor Instability: A Controlled Clinical Pilot Study, *Journal of Clinical and Experimental Gerontology*, 1987; 9:265-270.
36. Benvenuti F, Baroni A, Bandinelli S, et al, Flunarizine-induced Parkinsonism in the Elderly, *Journal of Clinical Rheumatology*, 1988; 158:600-608.

37. Burgio KL, Whitehead WE, and Engel BT, Urinary Incontinence in the Elderly: Bladder/Sphincter Biofeedback and Toileting Skills Training, *Ann Intern Med*, 1985; 103:507-515.
38. Tettenborn D, and Dycka J, Prevention and Treatment of Delayed Ischemic Dysfunction in Patients with Aneurysmal Subarachnoid Hemorrhage, *Stroke*, 1990; 21(sup 4): 85-89.
39. Tomberg T, and Magi M, Effect of Calcium Antagonists on Cerebral Blood Flow in Acute Stage of Cerebral Infarction, *J Neurol*, 1990; 237:138-141.
40. Pozzilli C, DiPiero V, Pantano P, et al, Influence of Nimodipine on Cerebral Blood Flow in Human Ischemia, *J Neurol*, 1989; 236:199-202.
41. Schuurman T, Klein H, Beneke M and Traber J, Nimodipine and Motor Deficits in the Aged Rat, *Neurosci Res Commun*, 1987; 1:9-15.
42. Deyo RA, Straube KT, and Disterhoft JF, Nimodipine Facilitates Trace Conditioning of the Eye-blink Response in Aging Rabbits, *Science*, 1989; 243:809-811.
43. Tollefson GD, Short-term Effects of the Calcium Channel Blocker Nimodipine (bay-e-9736) in the Management of Primary Degenerative Dementia, *Biol Psychiatry*, 1990; 27:1133-1142.
44. Ulrich G, Stieglitz RD, Effect of Nimodipine Upon Electroencephalographic Vigilance in Elderly Persons with Minor Impairment of Brain Functions, *Arzneimittel-Forschung*, 1988; 38:392-396.
45. Konrad-Dalhoff I, Baunack AR, Ramsch KD, et al, Effect of the Calcium Antagonists Nifedipine, Nitrendipine, Nimodipine and Nisoldipine on Oesophageal Motility in Man, *Eur J Clin Pharmacol*, 1991; 41:313-316.
46. Jansen I, Tfelt-Hansen P, and Edvinsson L, Comparison of the Calcium Entry Blockers Nimodipine and Flunarizine on Human Cerebral and Temporal Arteries: Role in Cerebrovascular Disorders, *Eur J Clin Pharmacol*, 1991.
47. Holstege G, Neuronal Organization of Micturition, *Neurourol Urodynam*, 1992; 11:273-277.
48. Griffiths DJ, McCracken PN, Moore K, et al, Location of Lesions Responsible for Geriatric Urge Incontinence, *Neurourol Urodynam*, 1992; 11:422-423.
49. Elliot RA, Norman RI, Parker SG, et al, Effect of treatment with calcium antagonists in vitro and in vivo on the contractile response of isolated rat and human detrusor muscle, *Clin Sci*, 1996;91:467-474

50. Kirch W, Ramsch KD, Duhrsen U and Ohnhaus EE, Clinical Pharmacokinetics of Nimodipine in Normal and Impaired Renal Function, *International Journal of Clinical Pharmaceutical Research*, 1984; 4:381-384.
51. Rud T, Andersson KE, and Ulmsten U, Effects of Nifedipine in Women with Unstable Bladders, *Urol Int*, 1979; 34:421-429.
52. Feinstein AR, *Clinometrics*, 1987; New Haven CT: Yale University Press
53. Wyman JF, Choi SC, Harkins SW, et al, The Urinary Diary in the Evaluation of Incontinent Women: A Test-retest Analysis, *Obstet Gynecol*, 1988; 71:812-817.
54. Norton C, The Effects of Urinary Incontinence in Women, *Int Rehab Med*, 1982; 63:9-14.
55. Wyman JF, Harkins SW, Choi Sc, et al, Psychosocial Impact of Urinary Incontinence in Women, *Obstet Gynecol*, 1987; 70:378-381.
56. Uebersax JS, Wyman JF, Shumaker SA, et al, Short Forms to Assess Life Qualith and Symptom Distress for Urinary Incontinence in Women: The Incontinence Impact Questionnaire and the Urogenital Distress Inventory. *Neurourol Urodyn* 1995;14:131-139
57. Barry MJ, Fowler FJ Jr., O'Leary MP, et al, The American Urological Association symptom index for benign prostatic hyperplasia. *J Urol* 1992;148:1549-1557
58. Chancellor MB, and Rivas DA, American Urological Association Symptom Index for Women with Voiding Symptoms: Lack of Index Specificity for Benign Prostate Hyperplasia, *J Urol*, 1993;150:1706-1709
59. McGuire EJ, Disorders of the control of bladder contractility. In: Kursh ED, McGuire EF, editors. *Female urology*. Philadelphia: Lippincott;1994. P.75-82
60. Jones B, and Lewis JA, The case for cross-over trials in phase III, *Statistics in Medicine*, 1995;14:1025-1038
61. Folstein F, Folstein S, and McHugh P, "Mini-Mental State". A Practical Method for Grading the Cognitive State of Patients for the Clinician, *J Psychiatry Res*, 1975; 12:189-198.
62. Guyatt GH, Deyo RA, Charlson M, et al, Responsiveness and Validity in Health Status Measurement: A Clarification. *J Clin Epidemiol*, 1989;42:403-408
63. Grimby A, Milsom I, Molander U, et al. The influence of urinary incontinence on the quality of life of elderly women. *Age Aging* 1993;22:82-89

64. Rosner B, Fundamentals of Biostatistics, Third Edition, PWS-Kent, Boston, Ms, 1990; 351-352.
65. Donner A, Approaches to Sample Size Estimation in the Design of Clinical Trials - A Review, *Statistics in Medicine*, 1984;3:199-217
66. Woods JR, Williams JG and Tavel M, The two-period crossover design in medical research, *Ann Int Med*, 1989;110:560-566
67. Jones and Kenward MG, *The Design and Analysis of Cross-over Trials*, Chapman and Hall, London, 1989
68. Willan AR, Using the maximum test statistic in the two-period cross-over trial, *Biometrics*, 1988;44:211-218
69. Grizzle JE, The two-period change over design and its use in clinical trials, *Biometrics*, 1965;21:467-480
70. Brown BW, The crossover experiment for clinical trials, *Biometrics*, 1980;36:69-79
71. Senn SJ, Cross-over trials, carry-over effects and the art of self delusion, *Statistics in Medicine*, 1988;7:1099-1101
72. Freeman PR, The performance of the two-stage analysis of two-treatment, two period cross-over trials, *Statistics in Medicine*, 1989;8:1421-1432
73. Kenward MG and Jones B, The analysis of data from 2X2 cross-over trials with baseline measurements, *Statistics in Medicine*, 1987;6:911-926
74. Willan AR, and Pater JL, Carry-over and the two-period cross-over clinical trial, *Biometrics*, 1986;42:593-599
75. Pahor M, Guralnik JM, Corti MC et al, Long term survival and use of antihypertensive medications in older persons, *J Am Geriatr Soc* 1995;43:1191-1197
76. Psaty BM, Heckbert SR, Koepsell TD, et al, The Risk of Myocardial Infarction Associated With Antihypertensive Drug Therapies, *JAMA*, 1995;274:620-625
77. SHEP Cooperative Research Group, Prevention of Stroke by Antihypertensive Drug Treatment in Older Persons With Isolated Systolic Hypertension, Final Results of the Systolic Hypertension in the Elderly Program (SHEP), *JAMA* 1991;265:3255-3264
78. Lee PS, Reid DW, Saltmarche A, et al. Measuring the Psychosocial Impact of Urinary Incontinence: The York Incontinence Perceptions Scale (YIPS), *J Am Geriatr Soc*,

1995;43:1275-1278

79. Yu LC, Kaltreider DL, Hu T, et al. The ISQ-P Tool: Measuring Stress Associated with Incontinence, *J Geront Nurs*, 1989;15:9-15
80. Pahor M, Guralnik JM, Furberg CD, et al. Risk of gastrointestinal hemorrhage with calcium antagonists in hypertensive persons over 67 years old. *Lancet* 1996;347:1061-1065
81. Pahor M, Guralnik JM, Salive ME et al. Do calcium channel blockers increase the risk of cancer: *Am J Hypertens* 1996;9:695-699
82. Legault C, Furberg C, Wagenknecht LE, et al, Nimodipine neuroprotection in cardiac valve replacement. Report of an early terminated trial. *Stroke* 1996;27:593-598
83. The Therapeutics Initiative, Review and Update 1996, *Can J Clin Pharmacol*,1997;4:12-14
84. Thomas DR, and Ritchie CS, Preoperative assessment of older adults, *J Am Geriatr Soc*, 1995;43:811-821
85. Szonyi G, Collas DM, Ding YY, Malone-Lee JG. Oxybutynin with Bladder Retraining for Detrusor Instability in Elderly People: A Randomized Controlled Trial, *Age and Aging*, 1995;24:287-291

Appendix A

NIMODIPINE FOR URGE INCONTINENCE RESEARCH PROJECT

Baseline Assessment:

Date Seen: _____

Name: _____ Screen No. _____ Entry No. _____

Date of Birth: _____ Age _____ Sex 1 male 2 female

Residence 1 home/apartment 2 senior's apartment 3 retirement home

Allergies 1 yes 2 no if yes, to what _____

Adverse reaction _____

Incontinence History:

1. Onset 1 sudden 2 gradual
2. Duration 1 < 6 months 2 6 months to 1 year 3 1-2 years
4 2-5 years 5 > 5 years
3. Incontinence over the past 6 months 1 worsening 2 stable
3 improving 4 fluctuates
4. How frequently do you go to the toilet during the day?
1 every hour or less 2 every 1 to 2 hours 3 every 2 to 3 hours
4 every 3 to 4 hours 5 every 4 to 6 hours
5. Do you have urine leakage during the waking hours? 1 yes 2 no
 - 5.1 if yes, how often 1 3 or more times a day 2 2 to 3 times/day
3 1-2 times a day 4 once a day
5 2-6 times a week 6 once a week
7 less than once a week
 - 5.2 if yes, how much 1 wet underwear only 2 wet outer clothing
3 run down your legs 4 pool on the floor
5 amount varies 6 contained

6. How frequently do you empty your bladder after going to bed?
 1. 0 2. 0-1 3. 2-3 4. >3
7. Do you have any urine leakage at night? 1 yes 2 no
- 7.1 if yes, how often 1 3 or more times a night 2 2 to 3 times/night
 3 1-2 times a night 4 once a night
 5 2-6 times a week 6 once a week
 7 less than once a week
- 7.2 if yes, how much 1 incontinent product 2 night attire
 3 plus bedding 4 plus more
8. Do you leak urine with physical stress?
 e.g., cough, laugh, sneeze, lift, jump, etc. 1 yes 2 no
 or just after? 1 yes 2 no
9. On average, how long can you hold on after feeling first urge to void?
 1 not at all 2 <30 seconds 3 30 seconds to 2 minutes
 4 2 to 5 minutes 5 5 to 15 minutes 6 >15 minutes 7 varies
10. Do you have 1 yes 2 no 3 don't know
 hesitancy
 straining/manual expression
 poor stream
 dysuria
 post micturition dribble
 constant dribble
 change in the odour of urine in the past 6 months
 hematuria
 prolapse
 intermittent stream
 frequency
11. Are you aware of the desire to void? 1 yes 2 no 3 varies
12. Are you aware of urine being passed? 1 yes 2 no 3 varies
13. Are you aware of being wet when urine leakage occurs?
 1 yes 2 no 3 varies
14. Are pads, pants, bed pads, external devices, etc., used?
 1 yes 2 no

if yes, describe number and type

while awake _____

while in bed _____

are they effective? 1 always 2 usually 3 sometimes 4 never

who buys the necessary product? 1 self 2 other

cost of product per month 1 \$1-25 2 \$26-50 3 \$51-100 4 >\$100

is the cost of products a financial burden to you? 1 yes 2 no

15. How often does your laundry have to be done?

1 every 2 weeks 2 every week 3 every 4-5 days
4 every 2-3 days 5 daily 6 more than once daily

16. Who does the laundry? 1 self 2 other

Fluid Intake:

17. Do you restrict your fluids? 1 yes 2 no 3 sometimes

18. How much do you drink in a day, including water?

breakfast _____
morning _____
lunch _____
afternoon _____
dinner _____
evening _____
total _____

1 <1 litre 2 1-1.5 litres 3 1.5-2 litres
4 2-2.5 litres 5 2.5-3 litres 6 >3 litres

Risk Behaviours:

19. Do you drink beverages containing caffeine? 1 yes 2 no
if yes, how much _____ mls/day

20. Do you drink alcoholic beverages? 1 yes 2 no
if yes, number/week _____

21. Have you ever used tobacco? 1 yes 2 no
 if yes, current? 1 yes 2 no
 amount _____ pack years
 if not current, quit when _____

Bowels:

22. What is your usual bowel pattern in the last 6 months?
 1 2-3 bms a day 2 1 bm a day 3 3-4 bms a week 4 2 a week or less
23. Do you frequently have hard or difficult bowel movements? 1 yes 2 no
 if yes, how often per month _____
24. Diet, fibre, or stool softeners used for regulation? 1 yes 2 no
25. Laxatives used for regulation? 1 yes 2 no 3 occasionally
 if yes, or occasionally, describe product and frequency

26. Do you frequently have loose bowel movements? 1 yes 2 no
27. Any blood in bowel movements in the past year? 1 yes 2 no
28. Have you ever had fecal incontinence in the last year?
 1 yes 2 no
 if yes, how often _____

Medical History:

- Have you ever had (circle if positive) 1 yes 2 no 3 unsure, NA
29. Diabetes
30. CVA/TIA
31. Parkinson's
32. Hypertension/PVD/MI/Angina
33. Heart Failure
34. Irregular heartbeat/Pacemaker
35. Spinal cord injury/Multiple sclerosis
36. Emphysema/COPD/Chronic bronchitis
37. Glaucoma/loss of vision/cataracts
38. Falls within the last year (number)/Broken Hip
39. Cancer (type)
40. Dementia/Alzheimer's
41. Arthritis involving back/hips/knees or ankles

Surgical/Urologic History:

Have you ever had (circle if positive)

- 42. TURP or other prostate surgery
- 43. Urinary retention
- 44. Kidney stones
- 45. UTI or pyelonephritis
- 46. Abdominal surgery
- 47. Vaginal repair
- 48. Hysterectomy
- 49. Bladder repair
- 50. Vaginal delivery, uncomplicated (number)
- 51. Vaginal delivery, forceps/breech/posterior/tears (number)
- 52. Caesarian section (number)
- 53. Describe in order any previous treatments for incontinence

Medications:

List all medications currently taking - prescription and OTC

Classification of medications (circle if positive)

- 54. anticholinergic
- 55. cholinergic
- 56. a-blocker
- 57. a-agonist
- 58. beta-blocker
- 59. diuretic
- 60. estrogen
- 61. sedative/hypnotic
- 62. tricyclic antidepressant
- 63. other antidepressant
- 64. antispasmodic

65. total number of drugs taken regularly _____
 66. total number of drugs taken prn _____

Social:

67. Do you live 1 alone 2 with spouse/partner 3 with relatives/friends
 68. Do you have ready access to a toilet/commode/urinal/bedpan?
 1 yes 2 no
 69. How serious do you think your urine leakage is?
 1 very 2 moderately 3 not very 4 not at all

Physical Examination:

70. Vision - able to read voiding record 1 yes 2 no
 - best single eye line on Snellen chart at 14" _____
 71. Hearing - able to hear finger rub at 8 cm in one ear 1 yes 2 no
 72. Blood pressure - standing _____
 lying _____
 73. Pulse _____
 74. Height _____ cm
 75. Weight _____ kg
 76. Body Mass Index _____
 77. Asymmetric tone or power, left versus right arm 1 yes 2 no
 78. Asymmetric tone or power, left versus right leg 1 yes 2 no
 79. Hand or head tremor at rest 1 yes 2 no
 80. Barthel Index Score _____
 81. IADL score _____

Vaginal/Genital - Female:

82. Circumvaginal muscle strength (to be done at time of in and out cath)

1 absent 2 slight 3 moderate 4 firm 5 not done

if absent, is bulbocavernosus reflex present? 1 yes 2 no

83. Have you ever sought medical advice for your bladder problem?

1 yes 2 no

Comment:

84. Cystocele 1 yes 2 no
if yes, GRADE I II III IV

85. Uterine prolapse 1 yes 2 no

86. Rectocele/Enterocoele (circle if present)

87. Atrophic vaginitis 1 yes 2 no

88. Vaginal discharge 1 yes 2 no
if yes, swab sent 1 yes 2 no

Genital - Male:

89. Epispadias/Hypospadias/Retracted Penis 1 yes 2 no

90. Prostate 1 yes 2 no 3 not done

tender or nodular 1 yes 2 no

enlarged 1 yes 2 no

Rectal Examination:

91. Perianal sensation 1 normal 2 reduced 3 absent

92. Anal tone 1 normal 2 reduced 3 absent

93. Perianal skin 1 normal 2 redness 3 breakdown

Appendix B

CYSTOSCOPIC AND URODYNAMIC EVALUATION

Cystoscopy:

Patients will be prepared and draped in the lithotomy position. 2% Lidocaine jelly without epinephrine will be instilled into the urethra. A 17 French cystoscope will be passed into the bladder. Using both a 30 and 70 degree lens, the urethra and bladder will be inspected. Urethral strictures, prostatic obstruction, infection and bladder cancer will be looked for. Bladder trabeculation will be noted and recorded as either 0, 1+, 2+, or 3+.

Multichannel Urodynamics:

Multichannel urodynamic equipment will be used. This equipment is available at both the Baycrest Geriatric Centre and The Toronto Hospital. A 14 French Foley catheter will be inserted into the bladder with a 4 French bladder pressure catheter. The 14 French Foley catheter will be used for fluid infusion. The bladder pressure catheter will measure intravesical pressure. A rectal balloon catheter will be inserted to measure intraabdominal pressure. Detrusor pressure will be determined by subtracting rectal pressure from vesical pressure. The patient will then be placed in the sitting position for the filling phase. The filling phase will involve an infusion rate of normal saline at 25 to 50 cc's per minute. The patient will undergo provocative testing, which includes fast fill, tap water running, hand in warm water, and standing or walking in the same spot. Instability or hyperreflexia will be defined, according to the International Continence Society, as a rise in detrusor pressure greater than or equal to 15 cms of water. Urge incontinence will be defined as urinary leakage with bladder instability or hyperreflexia. Compliance and

sensation will also be recorded. Compliance will be defined according to the international Continence Society. The flow phase will then be performed. The 14 French Foley catheter is removed and the bladder pressure catheter is left in place. The flow rate, volume voided and the residual will be recorded. Maximum opening pressure at the beginning of voiding will also be recorded. Stress incontinence will be determined by clinical history and by coughing and straining in both the supine and standing position with a full bladder.

Appendix C
 PERIOD R1 R2 A W B

VOIDING RECORD

SCREEN # _____
 ENTRY # _____

Please complete beginning:

	DAY 1		DAY 2		DAY 3		DAY 4		DAY 5	
	TOILET	WET								
MORNING 6 AM TO 12 NOON										
AFTERNOON 12 NOON TO 6 PM										
EVENING 6 PM TO MIDNIGHT										
OVERNIGHT MIDNIGHT TO 6 AM										

Mark with an X in the "TOILET" column each time you pass urine in the toilet.

Mark with an X in the "WET" column when you have any urine leakage.

Mark the time when you go to bed and when you get up in the morning.

Appendix D - Incontinence Impact Questionnaire

PERIOD R1 R2
A W B

IMPACT QUESTIONNAIRE

SCREEN # _____
ENTRY # _____

FOR EACH QUESTION, PUT AN X IN ONE BOX. CHOOSE THE BOX THAT BEST DESCRIBES HOW MUCH YOUR URINE PROBLEM HAS AFFECTED THAT ACTIVITY DURING THE PAST WEEK.

	NEVER	LESS THAN ½ THE TIME	ABOUT ½ THE TIME	MORE THAN ½ THE TIME	ALWAYS	DOESN'T APPLY TO ME
1. How often does your urine problem affect your ability to do your cooking, housework, yardwork or laundry?						
2. How often does your urine problem affect your shopping?						
3. How often does your urine problem affect your hobbies or exercise?						
4. How often does your urine problem affect what you do for entertainment (movies, concerts, dancing)?						
5. How often does your urine problem affect you when you travel in a bus, subway, or car?						
6. How often does your urine problem affect you when you go to a place where you don't know where the washrooms are?						
7. How often does your urine problem affect your going to church, temple or synagogue?						
8. How often does your urine problem affect your work or volunteer work?						
9. How often does your urine problem affect having friends visit?						
10. How often does your urine problem affect going out with friends?						
11. How often does your urine problem affect your relationships with your spouse or family?						

12.	How often does your urine problem affect how you dress?						
13.	How much does your urine problem make you worry about your physical health?						
14.	How much does your urine problem make you worry about your nerves or mental health?						
15.	Does your urine problem make you not do things for fear of smell?						
16.	Does your urine problem make you not do things because you are embarrassed?						
17.	Does your urine problem prevent you from getting enough sleep?						

POST-TREATMENT QUESTIONS

18. How does the number of times you leak urine now compare to before you received the medicine?

MUCH WORSE	A LITTLE WORSE	ABOUT THE SAME	A LITTLE BETTER	MUCH BETTER	DOESN'T APPLY TO ME

19. How does the amount of urine you leak now compare to before you received this medicine?

MUCH WORSE	A LITTLE WORSE	ABOUT THE SAME	A LITTLE BETTER	MUCH BETTER	DOESN'T APPLY TO ME

20. How does the urgency to empty your bladder now compare to before you received this medicine?

MUCH WORSE	A LITTLE WORSE	ABOUT THE SAME	A LITTLE BETTER	MUCH BETTER	DOESN'T APPLY TO ME

Appendix E - American Urologic Association Symptom Score

PERIOD R1 R2 A W B

AUA SYMPTOM SCORE

SCREEN # _____

ENTRY # _____

QUESTION	Not at all	Less than one time in five	Less than half the time	About half the time	More than half the time	Almost always
1. Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?						
2. Over the past month, how often have you had to urinate again less than two hours after you finished urinating?						
3. Over the past month, how often have you found you stopped and started again several times when urinating?						
4. Over the past month, how often have you found it difficult to postpone urination?						
5. Over the past month, how often have you had a weak urinary system?						

6. Over the past month, how often have you had to push or strain to begin urination?						
7. Over the past month, how many times did you most typically get up to urinate from the time you went to be at night to the time you got up in the morning?						

QUALITY OF LIFE ASSESSMENT

QUESTION	Delighted	Pleased	Mostly satisfied	Mixed	Mostly dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?	0	1	2	3	4	5	6

Appendix F

ADVERSE EFFECTS QUESTIONNAIRE

During the last 3 weeks, have you noticed any	Yes	No	If yes, describe
dizziness?			
lightheadedness or feeling faint?			
fatigue?			
nausea or vomiting?			
diarrhea?			
abdominal pain?			
drowsiness?			
insomnia?			
headache?			
confusion?			
rash or itchy skin?			
changes in your vision?			
joint pain or swelling?			
muscle pain or cramps?			
pain on urination?			
constipation?			
swelling of the legs or hands?			
shortness of breath?			
chest pain or heartburn?			
palpitations?			

Have you noticed any other changes that you think may be side effects of the pills you are taking?
 If so, describe _____

Questionnaire will be self-administered, with a research technician available to answer questions. Patients will be instructed to answer all questions, and will return questionnaire to the research technician when complete.

CLINICAL INFORMATION SHEET

The study will show whether nimodipine can improve the symptoms of urge incontinence in patients 65 years of age and older.

Nimodipine has been studied in several thousand patients with many conditions, including strokes, with a very good safety record. Nimodipine may have a beneficial effect on the bladder, and may improve symptoms of incontinence. Side effects from nimodipine are uncommon, and mild. If they occur, they are usually due to a lowering of the blood pressure, which can cause dizziness and fatigue. This lowering of the blood pressure is the only side effect of nimodipine that has occurred more often than with placebo pills in previous studies.

Subjects who agree to participate will be followed carefully for side effects, and that if any time they develop side effects that may be due to the medication, the medication will be stopped.

The study begins with a two week period during which time subjects keep a careful record of every time they urinate. Subjects who are unable to keep this careful record will not continue with the study, but will instead be seen again by Dr. Radomski within two weeks, and will be treated as a regular patient.

The study will involve taking either nimodipine or placebo pills for three weeks, then no pills for two weeks, then the opposite pills (nimodipine or placebo) for three weeks.

The study will last 11 weeks. For 5 weeks subjects will be asked to keep a careful record of every time they urinate. Subjects will return to the clinic 5 times during the 10 weeks. On each of these visits, a questionnaire will be completed, which will take less than 30

minutes. On 2 of these visits, a short written test will also be completed, blood pressure will be taken and a catheter will briefly be inserted into the bladder, and immediately removed. Insertion of the catheter is necessary to determine the effect of the medication on the bladder. The two visits when the catheter is inserted will take less than 45 minutes.

Complete confidentiality will be kept regarding all information gathered during the study. Neither subject's names nor any other identifying particulars will be made available to anyone other than the investigators.

Subjects may refuse to participate without affecting the care they receive at any time.

INFORMED CONSENT FORM**NIMODIPINE TRIAL**

I have agreed to participate in a trial being conducted by Drs. Brymer, Naglie and Radomski at The Toronto Hospital. The study will show whether nimodipine can improve the symptoms of urge incontinence in patients 65 years of age and older. These symptoms include urine leakage, having to urinate frequently, and with little warning.

I have been told that nimodipine has been studied in several thousand patients with many conditions, including strokes, with a very good safety record. I understand that nimodipine may have a beneficial effect on the bladder, and may improve my symptoms. I understand that side effects from nimodipine are uncommon. If they occur, they are usually due to a lowering of the blood pressure, which can cause dizziness and fatigue. This lowering of the blood pressure is the only side effect of nimodipine that has occurred more often than with placebo pills in previous studies. I have been told that although the placebo pills appear identical to the nimodipine pills, they contain no active medication.

I have been told that some recent studies suggest that nifedipine, a drug which is similar to nimodipine, may be associated with a slightly increased risk of heart attack and death in individuals with heart disease or high blood pressure. I have also been told that these studies suggest that the risk may be associated with higher doses of the medication. I understand that although nimodipine is a different drug, it may also be associated with a slightly increased risk, because it is in the same class of drugs as nifedipine. I understand that a low dose of nimodipine is being used in this study, and that there is no specific evidence that this dosage is associated with any increased risk of heart attack or death.

I understand that I will be followed carefully for side effects, and that if at any time I develop side effects that may be due to the medication, the medication will be stopped.

I understand that the study begins with a two week period during which time I will keep a careful record of every time I urinate. I understand that if I am unable to keep this careful record, I will not continue with the study, but will instead be seen again by Dr. Radomski within two weeks, and will be treated as a regular patient.

I have been informed I will receive either nimodipine or placebo pills for three weeks, then no pills for three weeks, then the opposite pills (nimodipine or placebo) for three weeks.

I understand that my involvement in this study will last 11 weeks. For 5 weeks, I will be asked to keep a careful record of every time I urinate. I will return to the clinic 7 times during the 11 weeks. On each of these visits, I will complete a questionnaire, which will take less than 30 minutes. On 2 of these visits, I will also complete a short written test, will have my blood pressure taken, and will have a catheter briefly inserted into my bladder, and immediately removed. Insertion of the catheter is necessary to determine the effect of the medication on my bladder. The two visits when the catheter is inserted will take less than 45 minutes.

I understand that complete confidentiality will be kept regarding all information gathered about me during the study. I understand that neither my name nor any other identifying particulars will be made available to anyone other than the investigators or will appear in any publication without prior approval from me.

I understand that I may refuse to participate without affecting the care I receive. I also understand that if I enter the study, I may withdraw at any time without affecting my present or future care.

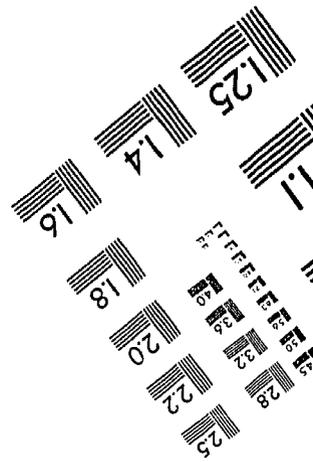
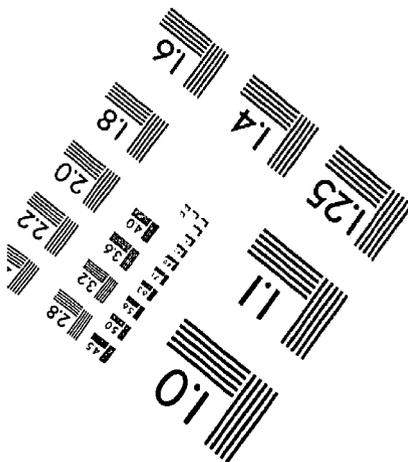
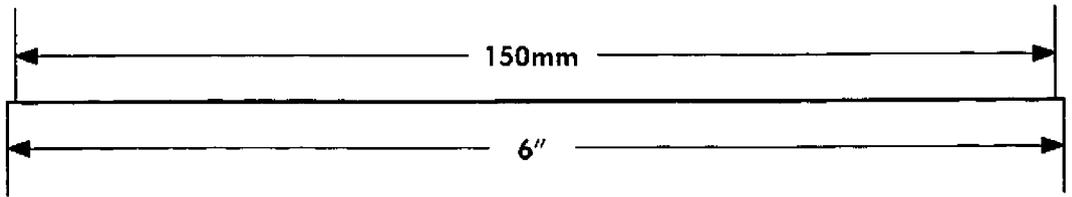
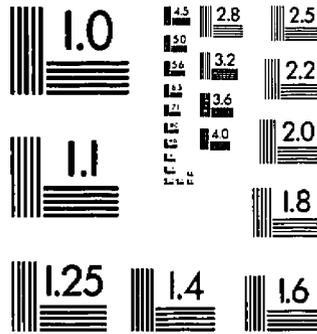
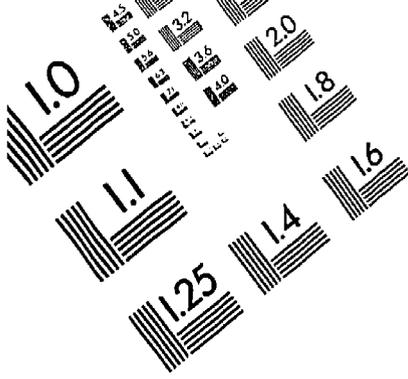
I understand that I will receive a copy of this consent form and that I may contact Dr. Naglie through the Research Office at The Toronto Hospital (340-4549) if I have any questions about the study.

Name of Participant (print) _____

Date _____

Signature of participant _____

Signature of witness _____



APPLIED IMAGE . Inc
1653 East Main Street
Rochester, NY 14609 USA
Phone: 716/482-0300
Fax: 716/288-5989

© 1993, Applied Image, Inc., All Rights Reserved