

Randomized Trial of Oxybutynin Extended Versus Immediate Release for Women Aged 65 and Older with Overactive Bladder: Lessons Learned from Conducting a Trial

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Abstract

Objective: This trial was designed to investigate the effectiveness of extended release versus immediate release oxybutynin in reducing symptoms of overactive bladder in a community-dwelling female population over the age of 65.

Methods: This was a prospective randomized 12-week, open-label study. The primary outcome was number of micturitions per 24 hours, 12 weeks after treatment. The a priori sample size estimate was 60 patients per group.

Results: Of the 318 women approached, only 72 women (23%) were enrolled over 34 months (33 in the immediate release group, and 39 in the extended release group). The study was stopped prematurely because of recruitment difficulties and an interim analysis revealing the need for a much larger sample than had been estimated to show a significant difference between treatments. After 12 weeks of treatment, there was no difference between the oxybutynin extended release and immediate release groups in the number of micturitions per 24 hours or in other outcomes.

Conclusion: This study did not demonstrate differences between oxybutynin extended release and immediate release and in reducing symptoms of overactive bladder or quality of life, possibly because the study did not reach the necessary sample size. The difficulty in recruiting subjects for the trial likely resulted from the onerous study requirements (4 study visits required over 12 weeks) and the downtown location of the study centres: these factors would cause particular difficulties for women over age 65 with overactive bladder, for whom travelling may be a problem. Evidence is needed to guide prescribing for older patients, but designing research to obtain adequate sample sizes is difficult.

Key Words: Overactive bladder, elderly, oxybutynin

Competing Interests: See Acknowledgements.

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Studies in older subjects should ensure that a much larger budget is allocated for recruitment than would be allocated for studies in younger subjects, that meticulous attention is paid to issues of transport and access, and that support is provided for subjects who agree to take part in research.

Résumé

Objectif : Cet essai a été conçu pour comparer l'efficacité de la libération prolongée de l'oxybutynine à celle de la libération immédiate en matière d'atténuation des symptômes de vessie hyperactive, au sein d'une population de femmes de plus de 65 ans demeurant au sein de la collectivité.

Méthodes : Il s'agissait d'une étude ouverte randomisée prospective de 12 semaines. Le principal critère d'évaluation était le nombre de mictions par 24 heures, 12 semaines à la suite du traitement. L'estimation de taille d'échantillon *a priori* était de 60 patientes par groupe.

Résultats : Seulement 72 (23 %) des 318 femmes sollicitées ont été admises à l'étude sur 34 mois (33 dans le groupe « libération immédiate » et 39 dans le groupe « libération prolongée »). Nous avons mis fin à l'étude de façon prématurée, en raison de difficultés de recrutement et des résultats d'une analyse intérimaire indiquant la nécessité d'avoir recours à un échantillon beaucoup plus vaste que ce que l'on avait estimé, afin de révéler une différence significative entre les traitements. Après 12 semaines de traitement, aucune différence n'a été constatée entre les groupes « libération immédiate » et « libération prolongée » en matière de nombre de mictions par 24 heures ou d'autres critères d'évaluation.

Conclusion : Cette étude n'a pas révélé de différences entre la libération prolongée d'oxybutynine et la libération immédiate en matière d'atténuation des symptômes de vessie hyperactive ou d'amélioration de la qualité de vie; ce résultat est peut-être attribuable à l'insuffisance de l'échantillon utilisé. Les difficultés quant au recrutement des sujets pour l'essai sont probablement attribuables aux lourdes exigences expérimentales (4 consultations d'étude requises sur 12 semaines) et à l'emplacement (centre-ville) des centres d'étude : ces facteurs

occasionnent des difficultés particulières aux femmes de plus de 65 ans présentant une vessie hyperactive, pour lesquelles les déplacements peuvent constituer un problème. Bien que nous ayons besoin de données pour guider les prescriptions offertes aux patientes âgées, la conception d'une étude permettant l'obtention de tailles d'échantillon adéquates s'avère ardue. Les études portant sur des sujets âgés devraient s'assurer d'allouer au recrutement un budget beaucoup plus important que celui qui y est alloué dans le cadre d'études portant sur de jeunes sujets, de porter une attention méticuleuse aux questions du déplacement et de l'accès, et d'offrir un soutien adéquat aux sujets qui consentent à participer à l'étude.

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INTRODUCTION

The International Continence Society defines OAB as a syndrome of symptoms characterized by urinary urgency and frequency and nocturia with or without urinary incontinence.¹ OAB is a common chronic condition that affects people of all ages, but particularly affects older women aged over 65.²⁻⁵ The prevalence of OAB in community-dwelling adults is approximately 30%,^{2,3} and even higher among institutionalized elderly adults.^{4,5} It has a significant impact on quality of life^{2,6}; individuals with OAB, regardless of urinary incontinence, have lower SF-36 scores, higher CES-D depression scores, and poorer quality of sleep scores.² Additionally, the presence of OAB is associated with an increased prevalence of other comorbidities and increased medical expenses involved in the management of those medical problems.^{7,8}

Different methods have been used to treat incontinence in elderly women, with the goal of improving their quality of life. Possible treatments include the use of diapers, prompted voiding, medications, electrical stimulation, bio-feedback, and indwelling catheters.⁹ At the time this study was initiated, the commonly used oral medications to treat OAB and urge incontinence were the anticholinergic

medications oxybutynin and tolterodine, in both short- and long-acting formulations.¹⁰ IR oxybutynin, generally given in three daily doses, was one of the first drugs used to treat OAB.¹⁰ Its use has been studied in institutionalized and geriatric patients, with conflicting results.¹¹⁻¹³ Because of its adverse effect profile, including dry mouth, constipation, blurred vision, and dizziness, many patients discontinued using it.¹⁰ The single dose XL oxybutynin has been shown to have comparable efficacy to oxybutynin IR in community-dwelling patients, with fewer adverse side effects.¹⁴⁻¹⁷ Oxybutynin XL has been studied in community-dwelling women with urge incontinence, but data from its use in women over the age of 65 are scarce.¹⁴⁻¹⁶

The goal of this study was to investigate whether the once daily administration of oxybutynin XL is more effective than the three times per day administration of oxybutynin IR in reducing symptoms of OAB, including urgency, frequency, and nocturia with or without urge incontinence, in a community-dwelling female population over the age of 65. Unfortunately the study was discontinued early, for two reasons. Firstly, the study experienced poor patient recruitment; secondly, an interim analysis of results indicated that the a priori sample size calculation, based on the anticipated difference in responses to treatment, did not reflect the sample in our study. We present here the design and results of the trial, and examine the lessons that were learned.

MATERIALS AND METHODS

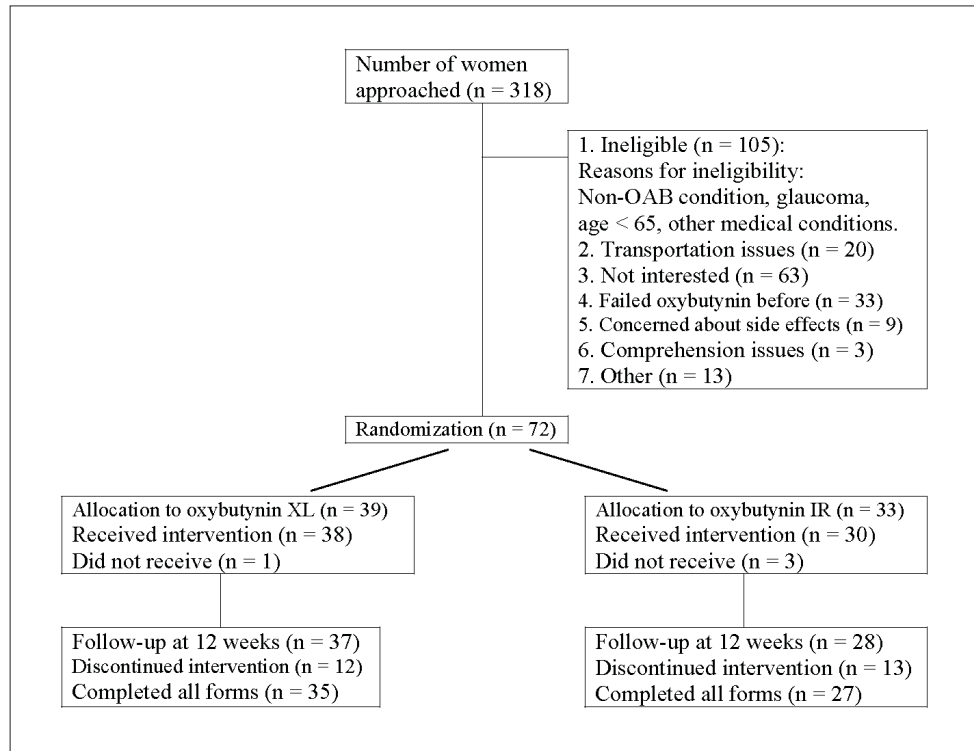
This was a prospective randomized open-label study comparing the effects of oxybutynin XL with those of oxybutynin IR in the treatment of women with overactive bladder. It was conducted at the Mount Sinai Hospital, a tertiary level Toronto teaching hospital, between February 2003 and December 2005. Community-dwelling patients presenting with symptoms of OAB to the urogynaecology units of Mount Sinai Hospital and the Baycrest Geriatric Centre in Toronto were recruited to the study. The inclusion criteria were being female and over the age of 65 with symptoms of OAB including urgency, frequency, and nocturia as defined by the International Continence Society¹; having mixed symptoms of OAB and stress urinary incontinence, with the former being the main presenting symptom; and being capable of providing written informed consent.

The exclusion criteria were being bedridden; having a permanent indwelling catheter; an MMSE score of less than 24¹⁸; incontinence due to causes other than predominant urge incontinence; evidence of glaucoma, gastric retention, or bowel obstruction; history of allergy to oxybutynin or anticholinergic drugs; taking tricyclic antidepressants or anticholinesterase inhibitors; having a post-void residual

ABBREVIATIONS

BMI	body mass index
IQR	interquartile range
IR	immediate release
MMSE	mini mental state examination
M-W	Mann-Whitney U test
OAB	overactive bladder
PVR	post-void residual
SD	standard deviation
SE	side effects
U-IIQ	urge-incontinence impact questionnaire
U-UDI	urge-urinary distress inventory
χ^2	chi-square test
XL	extended release

Flow of subjects through the trial



bladder volume of more than 100 mL; and a history of neurologic disorder such as multiple sclerosis, spinal cord injury, or demyelinating disorder.

Patients fulfilling the inclusion criteria were offered enrolment in the trial and were asked to give written consent to take part. A relevant medical history was taken from all patients. A focused physical and pelvic examination was performed that included testing the patient lying and standing for stress incontinence and staging of concurrent pelvic organ prolapse.¹⁹ Uroflowmetry and measurement of post-void residual bladder volume by ultrasound were performed. Patients found to have a urinary tract infection were treated with a one-week course of antibiotics prior to enrolment in the study.

Prior to randomization, the MMSE was administered. Subjects who scored 24 or more were eligible to continue with the study. Two validated quality of life questionnaires were administered to all participants at their initial visit: the 30-item U-IIQ, which assesses the impact of incontinence on quality of life with regard to activities, relationships, and feelings, and the nine-item U-UDI, which details symptoms of urine leakage and other bladder problems.²⁰ A three-day voiding diary was given to subjects to complete at home prior to the first treatment. Subjects who were on anticholinergic medications at the time of recruitment discontinued the treatment and underwent a two week wash-out.

Eligible subjects were randomly assigned to treatment with either oxybutynin XL once daily or oxybutynin IR three times daily for a total of 12 weeks. Random allocation was performed by a central telephone randomization service in order to reduce bias by concealing the sequence of allocation. Treatment allocation was carried out after patient recruitment and consent and immediately before initiating medical treatment. The research nurse contacted the randomization service to obtain the allocation. Subjects were randomized to receive either 5 mg of oxybutynin XL once daily or oxybutynin IR 2.5 mg three times daily. After four weeks of treatment, the dosage in non-responders was increased to 10 mg daily in the oxybutynin XL group and 5 mg three times daily in the oxybutynin IR group for an additional eight weeks. Non-responders were defined as those with a difference in mean daily frequency of urination between week one and week four of less than 1.5 according to the voiding diaries. Subjects were given sufficient medication and instructions about how to take the medication.

The primary outcome was the number of micturitions per 24 hours in each treatment group at 12 weeks after starting treatment. The number of micturitions in 24 hours was determined from the subjects' voiding diaries, completed prior to initiation of the study medication and at week 12. In addition, information was collected on the number of wetting episodes per day, the voided volume per micturition, and the number of pads used per day.

Other outcome measures included the scores obtained from the U-IIQ and U-UDI questionnaires at baseline and week 12 of treatment. Subjects were followed-up for 12 weeks, with a clinic visit at four weeks and a telephone follow-up at eight weeks. The main follow-up visit was at 12 weeks, when a three-day voiding diary was collected, and the quality of life questionnaires and MMSE were administered again. Uroflowmetry and measurement of post-void residual bladder volume by ultrasound were performed to ensure adequate bladder emptying.

Power calculation was performed as follows. Published voiding diary data suggest a standard deviation of three micturitions per 24 hours.²¹ Thus in order to have an 80% power to detect a difference of 1.5 in the number of micturitions per 24 hours at a two-tailed alpha level of 5%, a sample of 120 subjects (60 per group) was needed. Allowing for a drop-out rate of 10%, the estimated sample required was 132 (66 per group). This sample size would also enable us to detect a difference of 0.5 of the standard deviation in the secondary measures.

Data for all participants, including questionnaires, MMSE, voiding diaries, and consents, were included as part of the case report forms. The data were entered into the SPSS statistical package database (version 14.0, SPSS, Cary, NC) and analysis of data was conducted by “intent to treat.” For continuous variables, data were analyzed using the unpaired *t* test. For categorical variables, the Pearson chi-square and the Mann-Whitney-U tests were used. A *P* value of less than 0.05 was considered statistically significant. Data were analyzed to compare improvement in symptoms and quality of life between the groups.

Institutional approval was sought and obtained from the Mount Sinai Hospital and the Baycrest Geriatric Centre Research Review Boards. All patients were invited to give signed informed consent to participate in the study after reading the information sheet and being given the opportunity to discuss the trial with the research nurse and/or the study investigators. Participants were not paid but were reimbursed for their transportation and/or parking costs.

RESULTS

During the study period, 318 potentially eligible women were approached for possible participation in the trial. Of those, only 72 (23%) women over the age of 65 were enrolled into the study, 39 were randomized into the oxybutynin XL group and 33 into the oxybutynin IR group. The Figure shows the flow of patients in the study. The study was discontinued prematurely before reaching the sample size of 120 because of recruitment difficulties: we had recruited only 72 patients over a period of 34 months. Additionally, an interim analysis revealed that our patients

experienced a greater urinary frequency than anticipated, and the standard deviation was double what had been expected.

The baseline characteristics of the two groups are shown in Table 1. The groups were similar with respect to age, parity, body mass index, and urinary symptoms. Subjects in the oxybutynin XL group had a higher prevalence of fecal incontinence and positive cough test than those in the oxybutynin IR group. Subjects in the oxybutynin IR group had a higher prevalence of previous pelvic surgeries for incontinence and/or prolapse. Baseline scores on the MMSE, U-IIQ, and U-UDI were similar between the groups.

The primary and secondary outcomes for the two groups are shown in Table 2. At 12 weeks, there was no difference between the oxybutynin XL and IR groups with respect to the number of micturitions over 24 hours, number of pads used, voided volume per micturition, and post-void residual volume. There was within-group improvement in urinary frequency from week 1 to week 12, but no between-group difference. There was also no difference in the U-UDI, U-IIQ and MMSE at 12 weeks between the two groups. Seventy percent of those taking oxybutynin XL remained on the drug compared with 61% taking oxybutynin IR, but this difference was not significant. The side effect profile was similar in the two groups. All 25 subjects who stopped medication before week 12 did so because of side effects. The only marginally significant difference between groups was in the number of wetting episodes: women in the oxybutynin XL group experienced more wetting episodes than those in the oxybutynin IR group (Table 2).

DISCUSSION

This study was the first designed to evaluate the use of oxybutynin XL versus oxybutynin IR in older women, and it was carried out in an attempt to find the treatment that would provide the greatest reduction in the number of micturitions per day. In addition, we hoped to identify the treatment with fewest side effects, expecting that this would be the most acceptable treatment overall. The effect of treatment proved to be modest in both groups (a reduction of just over one voiding episode per day in women who voided on average 13 or 14 times per day at the start of the study) and did not differ statistically between groups. A substantial minority of patients had stopped medication before 12 weeks in both groups, all as a result of side effects of treatment. Unsurprisingly, there was therefore no difference in the quality of life reported in standard questionnaires and MMSE between the two groups.

Despite the disappointing results and our decision to stop the trial early, we learned significant lessons about

conducting randomized trials in elderly women with bladder control problems. The a priori decision about the difference in primary outcome used for the sample size calculation (a difference of 1.5 voids between groups) was based on data from the best available study of patients using oxybutynin.²¹ However, compared with the subjects enrolled in that study, our study subjects were older (74 vs. 61 years), were all female, and voided more frequently at baseline (13.6 vs. 11.6 mean voiding episodes per 24 hours). It is likely that our reliance on data that were not representative of our study population led to the underestimates of symptom prevalence and expected difference in outcome between treatment groups.

The feasibility of the study was based on our original sample size calculation, and the estimate that we would recruit 1.5 patients per week (from 5 eligible patients per week). In fact, during the three-year period of the study we screened approximately two patients per week, and recruited only 0.5 patients per week. If we had continued recruiting at the prevailing rate of recruitment, and on the basis of the interim analysis of results, it would have taken a further 205 months to reach the full sample size of 504. We considered asking other centres to collaborate in recruitment, but trial funding was limited, and to ask other centres to screen four patients per recruit and carry out study follow-up for 12 weeks without compensation would have been unrealistic.

We believe that our poor rate of recruitment was also a result of choosing to study patients in an older age group. Our study set out specifically to investigate the use of oxybutynin in women over the age of 65, because this was the group most likely to show benefit from treatment because of the increasing prevalence of OAB in older subjects.^{2,3} Moreover, results extrapolated from research done with younger people may not be applicable to older people.²² Previous research into incontinence had tended to avoid elderly patients.²²⁻²⁴ Oxybutynin is therefore under-prescribed in the elderly because of concerns about anticholinergic adverse events such as dry mouth, cognitive impairment, and sleep disturbances,²³ and lack of evidence to support its use.²⁴

Table 1. Baseline characteristics

	Oxybutynin XL n = 39	Oxybutynin IR n = 33
Age, mean years (SD)	75 (6)	73 (5)
Pregnancy history: parity, n (%)		
0	6 (15)	4 (12)
1	3 (8)	4 (12)
2	12 (31)	8 (24)
3 or more	18 (46)	17 (51)
Symptoms		
Frequency, median episodes (IQR)	9 (7-11)	10 (8-12)
Nocturia, median episodes (IQR)	2 (2-3)	3 (2-4)
Urgency, n (%)	39 (100)	32 (97)
Urge incontinence, n (%)	37 (95)	31 (94)
Stress incontinence, n (%)	26 (67)	17 (52)
Fecal incontinence, n (%)	9 (23)	3 (9)
Previous prolapse/incontinence surgery, n (%)	5 (13)	16 (49)
Height (cm), mean (SD)	158 (6)	159 (5)
Weight (kg), mean (SD)	73 (14)	76 (14)
BMI (kg/m ²), mean (SD)	29 (5)	30 (5)
Positive cough test, n (%)		
Lying	10 (26)	5 (15)
Standing	13 (33)	5 (15)
Pelvic Organ Prolapse*		
Cystocele, n (%) 0-1	27 (69)	22 (67)
2	8 (21)	6 (18)
3-4	4 (10)	5 (15)
Apex, n (%) 0-1	33 (85)	25 (76)
2	5 (13)	6 (18)
3-4	1 (3)	2 (6)
Rectocele, n (%) 0-1	26 (67)	24 (73)
2	9 (23)	7 (21)
3-4	4 (10)	2 (6)
Voiding diary, median (IQR)		
Voids/24hrs	13 (10-16)	14 (11-16)
Wetting episodes	2 (0-4)	1 (0-3)
Voided volume in cc	142 (109-192)	138 (108-165)
Pads/24 hrs	1 (0-3)	1 (0-3)
Mini-mental state exam, median score (IQR)	29 (29-30)	30 (28-30)
U-IIQ, mean score (SD)		
Activities	2.7 (0.9)	3.1 (1.1)
Travel	2.4 (1.3)	2.8 (1.6)
Physical activities	2.4 (1.2)	2.6 (1.5)
Feelings	2.5 (1.2)	2.7 (1.5)
Relationships	1.7 (0.6)	2.0 (1.4)
U-UDI, mean score (SD)	2.9 (0.6)	2.7 (0.8)
Urine culture positive, n (%)	3 (8)	3 (9)
Flow studies, median PVR (cc) (IQR)	0 (0-23)	0 (0-22)

*Staging was based on the Baden-Walker classification

Table 2. Outcomes at 12 weeks

	Oxybutynin XL n = 37	Oxybutynin IR n = 28	Statistical test
Primary Outcome			
Median number of micturitions per 24 hours at week 12 (IQR)	11 (9–13) (2 missing)	11 (9–14) (2 missing)	M-W 392, <i>P</i> = 0.35
Median change in 24 hour urinary frequency from week 1 to week 12 (IQR)	−1.4 (−3.3–+0.4) (2 missing)	−1.3(−4.1–+0.3) (3 missing)	M-W 408, <i>P</i> = 0.65
Other Outcomes			
Voiding function—at 12 weeks			
Median wetting episodes in 24 hours at week 12 (IQR)	1 (0–2) (3 missing)	0 (0–1) (2 missing)	M-W 316, <i>P</i> = 0.05
Median volume voided per micturition (IQR)	164 (129–187) (3 missing)	161 (114–109) (2 missing)	M-W 423, <i>P</i> = 0.78
Median number of pads per day (IQR)	0 (0–2) (3 missing)	0 (0–1) (2 missing)	M-W 402, <i>P</i> = 0.53
PVR in cc, median (IQR)	0 (0–29) (2 missing)	4 (0–87) (2 missing)	M-W 393, <i>P</i> = 0.33
Impact of urinary incontinence			
U-IIQ, mean score (SD)			<i>t</i> test
Activities	2.2 (1.0)	2.1 (1.2)	−0.35, <i>P</i> = 0.73
Travel	2.0 (1.1)	1.9 (1.2)	−0.27, <i>P</i> = 0.79
Physical activities	2.3 (1.3) (19 missing)	1.9 (1.2) (15 missing)	−0.77, <i>P</i> = 0.45
Feelings	2.0 (1.1)	1.9 (1.3)	−0.48, <i>P</i> = 0.63
Relationships	1.4 (0.9)	1.5 (1.0)	−0.24, <i>P</i> = 0.81
U-UDI, mean score (SD)			<i>t</i> test
	2.1 (1.0)	1.7 (1.0)	−1.68, <i>P</i> = 0.10
MMSE, median (IQR)	30 (29–30) (2 missing)	30 (29–30) (1 missing)	M-W 405, <i>P</i> = 0.62
Remain on medication at 12 weeks	26/37 (70%)	17/28 (61%)	χ^2 0.65, <i>P</i> = 0.42
Experienced SE			
Most common SE			
Dry mouth	14	16	
Gastro-intestinal	6	2	

Recruitment to clinical trials is always difficult.²⁵ However, research in older subjects is particularly difficult, especially when subjects are living in the community. Recruitment is time-consuming and costly, and advertisements are not very successful.²⁴ Many subjects need to be screened in order to recruit eligible patients (in the present study, we recruited only 23% of the patients we screened). Comorbidities lead to exclusion; this was the most common reason for patients being excluded from our study (30% of exclusions). Comorbidities can also result in high rates of attrition,²⁴ although this was not the case in our 12-week study.

The clinician can also hinder recruitment to trials unless he or she is completely committed to conducting the trial.²⁵ Less committed clinicians may be unwilling to make

additional demands on the patient, and clinicians may be less likely to offer participation in a trial to older patients than to younger patients.²⁶ That there were six physicians, each with a different level of interest in the trial, involved in seeing potentially eligible patients may have added to recruitment difficulties.

Our study made quite heavy demands on the participants, who were required to attend four study visits at the hospital over a 12-week period. This generally required travel to a downtown location with no patient parking. Public transportation is widely available but not easily accessible. We did not provide transportation or assistance, although parking and public transportation fees were paid if necessary.

Patients with OAB find it particularly difficult to travel because of urinary urgency

A study examining clinical trial recruitment strategies for older adults has made some suggestions for improving recruitment.²⁷ The authors suggested targeting groups who had high levels of health problems but who were reasonably active, such as residents of seniors' housing and clients of seniors' centres. They suggested providing incentives, especially providing transport and escorts for attending appointments, plus modest financial payments, because the elderly may have limited resources. In addition, they suggested reducing uncertainty for potential recruits by making presentations to seniors' groups about the study and seeking referrals from those already in the study.²⁷ We were unable to use such strategies because the resources for the study were constrained.

CONCLUSION

Our study indicates that oxybutynin had a modest impact on voiding symptoms in community-dwelling women over the age of 65, and that there were no statistically significant differences between oxybutynin IR and XL in reducing symptoms of OAB and its effect on the quality of life. It is possible that a larger study may have detected a significant difference between oxybutynin IR and XL groups. Evidence is clearly needed for prescribing for older patients, but research in this group is difficult. Future studies in older patients with OAB should bear in mind the lessons from our study: careful attention should be paid to the planning and design of the study, particularly making a detailed estimate of the number of eligible patients. Any study undertaken in older subjects should ensure that an adequate budget is allocated, that thorough recruitment strategies are in place, and that meticulous attention is paid to transportation, access, and support for subjects who agree to take part in research.

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