Patient factors associated with onabotulinum toxin A treatment outcome in women with detrusor overactivity

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Abstract

Objective

To evaluate potential predictors of non-response to treatment with 200U onabotulinum toxin A (onaBoNTA) in women with refractory detrusor overactivity (DO).

Subjects and Methods

A secondary analysis of a randomised trial of 200U onaBoNTA versus placebo in women with refractory DO analysed baseline and 6 week follow-up data. Univariate and multivariate logistic regression were used to assess demographic factors and baseline clinical parameters on non-response to treatment defined as 20% or less improvement in urinary urgency and leakage episodes, 10% or less in voiding frequency, not achieving continence, and “no change” or worse on PGI-I score at 6 weeks.

Results

122 women were included. 29 (23.8%), 24 (19.7%) and 19 (15.6%) were non-responders to treatment for urgency, voiding, and leakage episodes, respectively. 59 (48.4%) failed to achieve continence, and 28 (23%) were non-responders on the PGI-I scale. Smoking status (OR: 2.89 95% CI 1.08, 7.73, *p*=0.034) predicted non-response in urgency episodes, and higher baseline leakage episodes (OR: 1.17 95% CI 1.04,1.31, *p*=0.007) predicted non-response in achieving continence. Increasing age (OR 1.04, 95% CI 1.0, 1.09, *p*=0.063) and body mass index (BMI) (OR 1.07, 95% CI 1.0, 1.16, *P*=0.065) showed marginal associations with non-response on the PGI-I scale

Conclusion

onaBoNTA is an effective treatment for refractory DO, but some fail to respond. For identification of women at risk, our data indicate smokers should be advised of a lesser chance of successful treatment. Older women, those with high BMI and with more severe leakage also have a higher risk of failure.

250 words

Keywords

Onabotulinum toxin; detrusor overactivity; overactive bladder; treatment; efficacy

Introduction

Detrusor overactivity (DO) is characterised by spontaneous contractions of the detrusor muscle during bladder filling, causing symptoms of urgency, frequency, nocturia and incontinence, which together are symptoms of the overactive bladder syndrome (OAB)[1]. Initial treatments include behavioural therapy[2] and antimuscarinic drugs which have moderate efficacy but troublesome side effects leading to frequent discontinuations[3-6]. In the last five years, botulinum toxin A (BoNTA) has been rapidly adopted as a treatment for DO and OAB, based upon data from several case series and more recently several randomised trials which enrolled women with both urodynamically proven DO and those with only OAB symptoms[7-13]. The data from these trials consistently show profound and long lasting effects on all symptoms of OAB, typically with reductions in excess of 50% of baseline and duration of between three and nine months. However, not all patients respond to treatment with BoNTA, but very little data have been published exploring the reasons for this. Here we present a secondary analysis of data from a large single dose RCT comparing a dose of 200 units of onabotulinum toxin A (onaBoNTA) (BOTOX, Allergan USA) with placebo in women[11] to examine if any patient factors can predict the likelihood of treatment failure at six weeks after treatment. At the time to trial was conducted, 200 units of onaBoNTA was the accepted dose for patients with idiopathic DO, with the licences for 100 units only being granted after 2010.

Subjects and Methods

The RELAX trial[11] was registered on Current Controlled Trials (ISRCTN26091555) on 26th May 2005 and recruited between July 2006 and November 2009 from eight UK hospitals. The trial received ethical approval from the Scottish Multicentre Research Ethics Committee (ref: 04/MRE10/67). Briefly, women with proven DO on urodynamics[1] within two years of recruitment, at least eight voids and at least two “moderate” or “severe” urgency episodes per 24 hours[14], refractory to standard treatment were randomised 1:1 to receive 200 units of onaBoNTA (BOTOX®, Allergan USA) or placebo injected in 20 sites, sparing the trigone. This was the accepted dosage recommended for idiopathic DO worldwide during the lifetime of the trial. Blinded outcome data were collected at baseline, six weeks, three months (by post), and six months. Urinary voiding frequency, leakage episode frequency, urgency episode frequency (moderate or severe on Indevus Urgency Severity Scale (IUSS))[14] were recorded in 3-day voiding diaries; the International Consultation on Incontinence Questionnaire short form (ICIQ-SF)[15], Incontinence Quality of Life (IQOL) questionnaire[16], and Patient Global Impression of Improvement (PGI-I)[17, 18] scale were completed at each time point. Details of the trial design and primary study outcome data have been reported elsewhere[11]. The analysis presented here focussed on baseline and six-week follow up data from those women who received active drug. After six weeks follow up, the original trial protocol allowed women with little response to resume antimuscarinic medication, so this time point was the only opportunity to analyse the effects of onaBoNTA alone.

Statistical analysis

There is no agreed definition of “non-response” to any treatment for DO or OAB. To search for factors influencing the effect of onaBoNT-A in women receiving active drug we have defined non-response for each of the outcome measures used in the trial: 20% or less improvement in urgency episode frequency; 10% or less improvement in voiding episode frequency; 20% or less improvement in leakage episode frequency; those women not achieving continence, and those women reporting a response of “no change” or worse on the PGI-I scale[17]. These definitions represented a reduction of approximately one episode per day for the median of each variable at baseline: urgency (1.6), leakage (1.2) and voiding frequency (1.0) episodes[11]. We explored both primary and all secondary outcomes from the blinded trial in this analysis, due to the lack of a standardised definition of non-response. A sensitivity analysis was included to examine different cut-off thresholds (at 10% and 50%) in view of the absence of an agreed definition. All outcomes were studied at six weeks (first follow-up) to avoid confounding of the use of additional treatments (usually antimuscarinic drugs) which were allowed during the remainder of follow-up between six weeks and six months, and because the greatest treatment effect was seen at this time[11].

Relevant demographic factors and baseline clinical parameters were analysed in a complete case analysis using univariate logistic regression. Factors found to be significant at the 10% level in the univariate analysis were entered into stepwise forward multiple regression. Variables with p-values <0.05 were considered significant. The following potential factors were examined: age at treatment; body mass index (BMI); ethnicity; parity; smoking status; previous continence surgery; baseline voiding frequency; baseline leakage episodes; baseline urgency episodes; baseline Urgency Severity Score; baseline maximum voided volume from the urinary diary; baseline mean voided volume from the urinary diary; baseline ICIQ score; baseline I-QoL score; and baseline urodynamic data (including volume at first desire, volume at capacity, maximum detrusor pressure, maximum voiding detrusor pressure, maximum free flow rate, detrusor pressure at maximum flow). We also included the occurrence of urinary retention and urinary tract infection identified at the six week visit as additional, post-treatment factors which might influence perceived efficacy. All statistical analyses were performed using STATA, version 13.0 (StataCorp, College Station, TX, USA).

Results

415 women were screened and 240 were enrolled and treated in the randomised study[11]. 122 women were randomised to BoNTA and 118 women to placebo. All outcome data were comparable at baseline (data not shown) [11]. Of the 122 women receiving active treatment, 29 (23.8%) had a 20% or less change in urgency episodes at 6 weeks, 24 (19.7%) had a 10% or less change in voiding episodes at 6 weeks, 19 (15.6%) had a 20% or less change in leakage episodes at 6 weeks, 59 (48.4%) failed to achieve continence, and 28 (23%) reported a response of “no change” or worse on the PGI-I scale. Baseline characteristics studied for these women are presented in Table 1.

Univariate analysis identified smoking status as a potential predictor of non-response in urgency episodes, with smokers having nearly three times increased odds of non-response (OR:2.89 95% CI 1.08,7.73, p=0.034) compared to non-smokers. For every additional increase in baseline leakage episodes, patients had an 17% increased odds of failing to achieve continence (OR: 1.17 95% CI 1.04,1.31, p=0.007). At the 10% significance threshold, age, baseline voiding frequency, and I-Qol score were individually identified as potential predictors of non-response in voiding frequency. Age and BMI were associated with non-response on the PGI-I scale (Table 2).

Multiple characteristics were found to be associated with non-response in voiding frequency, and non-response on the PGI-I scale, and thus these factors were entered in to a multivariate analysis. Having accounted for all associated factors in a multiple regression, both increasing age (OR 1.04, 95% CI 1.0, 1.09, p=0.063) and BMI (OR 1.07, 95% CI 1.0, 1.16, p=0.065) showed a marginal association with non-response on the PGI-I scale. All other factors had a non-significant association with non-response in the presence of all other associated variables (Table 3).

The occurrence of voiding dysfunction or urinary tract infection had no effect upon the analyses above. In our sensitivity analysis, the cut-off of 10% or 50% did not alter the variables found to be significant in multivariate analysis.

Discussion

In this study we assessed potential patient factors that predicted non-response at 6 weeks after active treatment. Smoking status and baseline leakage episodes were strongly associated factors with non-response to BoNTA. It is not surprising that more severe incontinence is less likely to be resolved after treatment, and it seems reasonable to advise the severely incontinent patients that they may have some residual leakage. The way in which smoking may be acting is not clear. It is interesting to note that smoking does not appear to reduce the efficacy of antimuscarinic drugs[19], although it does increase the likelihood of discontinuation of oral medication[20]. It seems unlikely that an effect is acting via the nicotinic receptors in the parasympathetic ganglia, since onaBoNTA will be preventing the downstream release of neurotransmitter within the bladder. Smoking may be an indirect marker of cardiovascular changes leading to increased hypoxia in the bladder wall; episodes of hypoxia have been shown to increase detrusor contractility in vitro[21], and in the bladders of atherosclerotic rabbits, with related ischaemia[22, 23].

Several authors have also examined clinical factors predictive of cure, from studies using a range of doses. As mentioned above, during the conduct of the trial from which our results are taken, 200 units of onaBoNTA was the accepted dose. Sahai et al[24] analysed data from 33 patients enrolled in their randomised study of 200 units of onaBoNT-A or placebo[7], five of whom were deemed non-responders (based on patient reports and diary data, but not defined). Non-responsive patients had a significantly higher maximum detrusor pressure before treatment compared to responsive patients, but all other urodynamic factors were similar. Cohen et al[25] analysed data from 35 patients

with overactive bladder who received intradetrusor onaBoNTA injections (100 and 150 U). Their definition of response was a 40% or more improvement from baseline, compared to our definitions of 10% and 20% (equivalent to one episode per day), but they did not identify any predictive factors. Schmid et al[26] analysed 100 patients with idiopathic OAB receiving 100 units of BoNTA and found that low bladder compliance, on pre-operative urodynamic assessment, and a maximal cystometric capacity less than 100mL (confirmed on biopsy to be fibrosis),was seen in the eight patients who did not respond. Although our data did not confirm the findings from these two papers, it should be emphasised that these authors only conducted univariate analyses, so did not control for potential confounding between variables and did not explore the possibility of potential interactions. Our logistic regression accounts for this and so the data suggest that it is not possible to reliably identify patients who may fail to achieve benefit from onaBoNTA treatment.

It is interesting to note conflicting evidence on success rates related to antimuscarinic drug history. Makovey et al reported that following 150 -200 units of onaBoNTA success rates were lower in patients reporting lack of efficacy of antimuscarinic drugs (34 of 57, 68%), compared to those who stopped because of side effects (24 of 28, 86%)[27]. In contrast, a pooled analysis of two trials of 100 units onaBoNTA showed no difference in treatment effect irrespective of the number of antimuscarinic preparations tried, or whether oral medication was stopped due to side effects or lack of efficacy[28]. It may be a possibility that some patients have a more resistant disease state, but whether this is a motor or sensory phenomenon is unclear. We are not able to comment on whether predictors of success vary by treatment dose, but there is no physiological or pharmacological reason why such a difference would exist.

There are limitations to this study. As a result of the efficacy of active treatment, there were few non-responders in the study population. Increasing the number of predictive variables in the model can therefore be problematic and reduce the power of the logistic regression model[29]. There is no agreed definition of what constitutes non-response after onaBoNTA treatment, as can be seen by the different definitions of non-response in the papers above[24-26]. In order to address this perceived limitation, we explored varying definitions of non-response in a sensitivity analysis. We tested non-response set at 10% or less, and 50% or less improvement; however, this had very little impact on the overall conclusions made, and the results mirrored that of the 20% analysis.

Some authors consider voiding dysfunction to be a significant factor in poor outcome after treatment, based on the findings of Brubaker et al[8] and others[12]. We explored the influence of urinary retention and infection on non-response to treatment at six weeks, and found neither were independently associated. This is somewhat counter-intuitive so it may be that an assessment of efficacy at a longer interval would identify these as factors, but in the short term this does not appear to be the case. Due to the additional medication allowed after 6 weeks in our protocol, we are unable to assess this reliably.

A further limitation is the considerably large number of women with missing urodynamic data. Despite confirming the presence of detrusor contractions on the cystometry traces, 91 of the 122 (74.6%) had missing values for at least one of the baseline urodynamic factors. Where data were missing, the patient was excluded from the analyses involving that variable. To ameliorate the effect that this had on the complete case analysis we used multiple imputation techniques. We used multivariate normal regression to impute 10 datasets based on the data collected from the RELAX trial (inclusive of placebo patients); however, due to the limited urodynamic dataset in the original trial, there was considerable uncertainty in the imputed estimates and multiple imputation had very little benefit.

In conclusion, onaBoNTA is well established as a second-line treatment for patients with OAB and DO. However, not all women respond to treatment and being able to predict a patient's likelihood of response would be clinically and economically advantageous. Previous studies have suggested that maximum detrusor pressure, poor compliance, and low maximum cystometric capacity were predictors of non-response, and identified urinary retention and infection as potential factors. Our regression analysis did not confirm these observations but identified baseline leakage episodes and smoking status as further predictors of non-response to BoNTA in patients with refractory DO.

2,230 words

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Table 1a. Baseline clinical characteristics of the patients receiving botulinum toxin by change in urinary diary symptoms

	Change in urgency episodes <= 20%			Change in voiding frequency <= 10%			Change in leakage episodes <= 20%		
	Non-response	**Response**	**Missing**	**Non-response**	**Response**	**Missing**	**Non-response**	**Response**	**Missing**
Characteristics									
n (122)	29 (23.8%)	78 (63.9%)	15 (12.3%)	24 (19.7%)	86 (70.5%)	12 (9.8%)	19 (15.6%)	91 (74.6%)	12 (9.8%)
Age	59.8 (9.7)	59.3 (11.8)	60.2 (14.7)	63.2 (10.8)	58.8 (11.5)	57.3 (14.2)	62.2 (11.1)	59.3 (11.5)	57.3 (14.1)
Ethnicity									
White (n=117)	27 (93.1 %)	75 (96.2%)	15 (100%)	24 (100%)	81 (94.2%)	12 (100%)	18 (94.7%)	87 (95.6%)	12 (100%)
Other (n=5)	2 (6.9%)	3 (3.6%)	0 (0%)	0 (0%)	5 (5.8%)	0 (0%)	1 (5.3%)	4 (4.4%)	0 (0%)
Parity									
0 (n=10)	2 (6.9%)	6 (7.7%)	2 (13.3%)	3 (12.5%)	5 (5.8%)	2 (16.7%)	1 (5.3%)	7 (7.7%)	2 (16.7%)
1+ (n=122)	27 (93.1%)	72 (92.3%)	13 (86.7%)	21 (87.5%)	81 (94.2%)	10 (83.3%)	18 (94.7%)	84 (92.3%)	10 (83.3%)
Previous surgery									
Yes	12 (41.4%)	28 (35.9%)	4 (26.7%)	11 (45.8%)	30 (34.9%)	3 (25%)	9 (47.4%)	32 (35.2%)	3 (25%)
No	17 (58.6%)	50 (64.1%)	11 (73.3%)	13 (54.2%)	56 (65.1%)	9 (75%)	10 (52.6%)	59 (64.8%)	9 (75%)
BMI	30.4 (6.5)	28.5 (6.0)	29.0 (7.3)	30.3 (7.1)	28.6 (5.8)	29.5 (7.8)	31 (6.5)	28.5 (6.0)	29.5 (7.8)
Baseline leakage	6.5 (5.3)	6.4 (4.0)	6.8 (4.2)	6.0 (3.8)	6.5 (4.4)	7.4 (4.3)	7.5 (4.4)	6.1 (4.3)	7.4 (4.3)
Baseline urgency	7.4 (3.5)	8.2 (3.1)	8.6 (3.4)	7.1 (3.3)	8.2 (3.2)	9.2 (3.2)	7.8 (3.1)	8 (3.3)	9.2 (3.2)
Baseline voiding	13.9 (10.2)	11.7 (3.3)	11.0 (2. 7)	10.6 (2.0)	12.7 (6.6)	11.4 (2.9)	11.9 (3.3)	12.3 (6.4)	11.3 (2.9)
Smoking Status									
Smoker	10 (34.5%)	12 (15.4%)	8 (53.3%)	5 (20.8%)	18 (20.9%)	7 (58.3%)	6 (31.6%)	17 (18.7%)	7 (58.3%)
Non-smoker	19 (65.5%)	66 (84.6%)	7 (46.7%)	19 (79.2%)	68 (79.1%)	5 (41.7%)	13 (68.4%)	74 (81.3%)	5 (41.7%)
Max voided vol	375.1 (184.9)	387.9 (134.9)	316.5 (136.5)	376.5 (152.7)	385.3 (147.8)	309.2 (146.2)	384.2 (137.7)	383.2 (151.1)	309.2 (146.0)
Av. voided vol	166.5 (76.8)	171.6 (61.3)	169.2 (87.8)	173.0 (47.6)	168.7 (47.6)	173.4 (97.3)	170 (50.3)	169.5 (67.5)	173.4 (97.3)
IUSS score	2.0 (0.6)	2.0 (0.5)	2.1 (0.5)	2.0 (0.6)	2.0 (0.5)	2.2 (0.5)	2.1 (0.5)	2.0 (0.5)	2.2 (0.5)
ICIQ score	15.3 (4.5)	14.1 (9.9)	16.4 (4.6)	15.0 (4.8)	14.4 (9.5)	16.3 (5.1)	16.7 (2.7)	14 (9.4)	16.3 (5.1)
I-QoL score	24 (18.9)	21.3 (46.8)	24.9 (19.1)	33.3 (20.7)	18.4 (44.1)	28.8 (19.4)	29.8 (19.3)	19.6 (43.6)	28.8 (19.3)

Table 1b. Baseline clinical characteristics of the patients receiving botulinum toxin by continence status and Patient Global Impression of Improvement

	Incontinent at follow up			Patient Global Impression of Improvement		
	Non-response	**Response**	**Missing**	**Non-response**	**Response**	**Missing**
Characteristics						
n (122)	59 (48.4%)	45 (36.9%)	18 (14.8%)	28 (23.0%)	80 (65.6%)	14 (11.5%)
Age	61.3 (11.0)	58.4 (11.8)	56.6 (13.2)	63.7 (11.1)	59.0 (11.0)	54.5 (14.4)
Ethnicity						
White (n=117)	55 (93.2%)	44 (97.8%)	18 (100%)	26 (92.9%)	78 (97.5%)	13 (92.9%)
Other (n=5)	4 (6.8%)	1 (2.2%)	0 (0%)	2 (7.1%)	2 (2.5%)	1 (7.1%)
Parity						
0 (n=10)	2 (3.4%)	5 (11.1%)	3 (16.7%)	1 (3.6%)	6 (7.5%)	3 (21.4%)
1+ (n=122)	57 (96.6%)	40 (88.9%)	15 (83.3%)	27 (96.4%)	74 (92.5%)	11 (78.6%)
Previous surgery						
Yes	25 (42.4%)	14 (31.1%)	25 (42.4%)	14 (50%)	27 (33.8%)	3 (21.4%)
No	34 (57.6%)	31 (68.9%)	34 (57.6%)	14 (50%)	53 (66.3%)	11 (78.6%)
BMI	29.8 (6.5)	28.4 (5.4)	27.9 (7.6)	30.7 (6.1)	28.2 (5.7)	30.2 (9.0)
Baseline leakage	7.7 (4.4)	5.4 (3.4)	4.9 (5.0)	6.7 (5.6)	6.6 (4.0)	5.2 (2.7)
Baseline urgency	7.9 (3.4)	7.9 (3.3)	9.2 (3.1)	7.6 (3.5)	8.3 (3.4)	7.8 (2.2)
Baseline voiding	12.7 (7.5)	11.74 (3.6)	11.5 (2.5)	14.3 (10.3)	11.7 (3.3)	10.5 (1.9)
Smoking Status						
Smoker	11 (18.6%)	12 (26. 7%)	7 (38.9%)	7 (25%)	19 (23.8%)	4 (28.6%)
Non-smoker	48 (81.4%)	33 (73.3%)	11 (61.1%)	21 (75%)	61 (76.3%)	10 (71.4%)
Max voided vol	379.3 (141.7)	398.3 (161.6)	309.6 (126.5)	356.8 (180.5)	388.4 (136.0)	344.4 (154.1)
Av. voided vol	166.9 (72.3)	172.2 (56.2)	174.6 (84.9)	176.2 (99.9)	168.0 (56.2)	169.3 (56.0)
IUSS score	2.0 (0.5)	2.0 (0.5)	2.1 (0.5)	2.0 (0.6)	2.1 (0.5)	2.1 (0.4)
ICIQ score	16.2 (5.8)	13.8 (10.3)	11.9 (9.3)	15.7 (3.8)	14.5 (9.8)	13.9 (6.1)
I-QoL score	20.7 (33.9)	19.9 (49.0)	33.8 (22.6)	26.8 (21.1)	19.1 (45.4)	32.1 (22.2)

Table 1c. Baseline urodynamic characteristics of the patients receiving botulinum toxin by change in urinary diary symptoms

	Change in urgency episodes <= 20%			Change in voiding frequency <= 10%			Change in leakage episodes <= 20%		
	Non-response	**Response**	**Missing**	**Non-response**	**Response**	**Missing**	**Non-response**	**Response**	**Missing**
n (122)									
Cystometry data									
Volume at first sensation									
n(%miss)	15 (48.3%)	24 (69.2%)	9 (40%)	12 (50%)	27 (68.6%)	9 (25%)	7 (63.2%)	32 (64.8%)	9 (25%)
mean(SD)	116.1 (96.3)	128.5 (84.5)	74.7 (50.3)	119.35 (100.2)	125.7 (84.3)	74.7 (50.3)	141.6 (112.4)	119.8 (83.6)	74.7 (50.3)
Bladder capacity at cystometry									
n(%miss)	15 (48.3%)	26 (66.7%)	11 (26.7%)	12 (50%)	30 (65.1%)	10 (16.7%)	7 (63.2%)	35 (61.5%)	10 (16.7%)
mean(SD)	349.7 (125)	376.3 (126.8)	291.1 (114.2)	384.2 (96.8)	360.0 (133.9)	282.3 (116.4)	427.1 (107.2)	354.8 (124.7)	282.3 (116.4)
Maximum filling detrusor pressure									
n(%miss)	14 (51.7%)	26 (66.7%)	11 (26.7%)	12 (50%)	29 (66.3%)	10 (16.7%)	7 (63.2 %)	34 (62.6%)	10 (16.7%)
mean(SD)	27 (28.2)	21.67 (16.6)	39.9 (26.3)	20.4 (24.1)	25.4 (19.7)	41.3 (27.3)	22.43 (30.1)	24.24 (19.1)	41.3 (27.3)
Maximum voiding detrusor pressure									
n(%miss)	10 (65.5%)	23 (70.5%)	8 (46.7%)	8 (66.7%)	26 (69.8%)	7 (41.7%)	5 (73.7%)	29 (68.1%)	7 (41.7%)
mean(SD)	50.9 (23.2)	41.7 (16.3)	56 (25.4)	42.8 (21.3)	44.5 (18.1)	59.3 (25.6)	47.4 (21.9)	43.6 (18.3)	59.3 (25.6)
Detrusor pressure at max flow rate									
n(%miss)	10 (65.5%)	22 (71.8%)	6 (60%)	8 (66.7%)	24 (72.1%)	6 (50%)	5 (73.7%)	27 (70.3%)	6 (50%)
mean(SD)	39.2 (20.5)	34 (14.4)	36.5 (22.7)	33.6 (18.2)	36.3 (16.1)	36.5 (22.7)	34.6 (16.2)	35.9 (16.7)	36.5 (22.7)
Volume at time of first contraction									
n(%miss)	12 (58.6%)	24 (69.2%)	11 (26.7%)	10 (58.3%)	27 (68.6%)	10 (16.7%)	5 (73.7%)	32 (64.8%)	10 (16.7%)
mean(SD)	235.6 (176.1)	243.1 (162.8)	139.3 (117.0)	236.5 (163.8)	235.6 (168.7)	146.7 (120.5)	262.6 (218.2)	231.7 (159.3)	146.7 (120.5)
Amplitude of first contraction									
n(%miss)	12 (58.6%)	23 (70.5%)	11 (26.7%)	11 (54.2%)	25 (70.9%)	10 (1667%)	6 (68.4%)	30 (67%)	10 (16.7%)
mean(SD)	21.8 (8.2)	20.8 (14.6)	22.6 (16.3)	17.7 (7.4)	22 (14.5)	24.5 (15.9)	19.8 (7.4)	20.9 (13.7)	24.5 (15.9)

Table 1d. Baseline urodynamic characteristics of the patients receiving botulinum toxin by continence status and Patient Global Impression of Improvement

	Incontinent at follow up			**Patient Global Impression of Improvement**		
	Non-response	**Response**	**Missing**	**Non-response**	**Response**	**Missing**
n (122)						
Cystometry data						
Volume at first sensation (mls)						
n(%miss)	24 (59.3%)	13 (71.1%)	11 (38. 9%)	9 (67.9%)	27 (66.3%)	12 (14.3%)
mean(SD)	126 (94.3)	123 (86.4)	79.5 (46.3)	81.8 (60.3)	131.6 (94.7)	100.8 (68.1)
Bladder capacity at cystometry (mls)						
n(%miss)	25 (57.6%)	15 (66.7%)	12 (33.3%)	11 (60.7%)	29 (63.8%)	12 (14.3%)
mean(SD)	376.4 (138.7)	347.3 (105.8)	301.1 (114.)	360.1 (133.9)	367.1 (123.0)	302.2 (123.3)
Maximum filling detrusor pressure (cm H_20)						
n(%miss)	24 (59.3%)	15 (66.7%)	12 (33.3%)	11 (60.7%)	28 (65%)	12 (14.3%)
mean(SD)	24.4 (25.2)	24.4 (14.0)	36.9 (26.8)	31.7 (29. 7)	23.1 (17.3)	33.1 (28.1)
Maximum voiding detrusor pressure (cm H_20)						
n(%miss)	21 (64.4%)	12 (73.3%)	8 (55.6%)	9 (67.9%)	22 (72.5%)	10 (28.67%)
mean(SD)	42.5 (21.7)	45.8 (12.4)	59 (23.7)	52.6 (23.5)	42.1 (15.3)	51.5 (26.5)
Detrusor pressure at max flow rate (cm H_20)						
n(%miss)	21 (64.4%)	10 (77.8%)	7 (61.1%)	8 (71.4%)	21 (73.8%)	9 (35.7%)
mean(SD)	34.3 (17.7)	36.4 (13.3)	39.4 (22.1)	36.6 (22.0)	36.2 (13.3)	34.1 (22.1)
Volume at time of first contraction (mls)						
n(%miss)	20 (66.1%)	15 (66.7%)	12 (33.3%)	10 (64.3%)	25 (68.8%)	12 (14.3%)
mean(SD)	255.5 (184.4)	202.9 (140.1)	170 (133.3)	191 (155.5)	239.5 (163.0)	191.4 (163.0)
Amplitude of first contraction (cm H_20)						
n(%miss)	19 (67.8%)	15 (66.7 %)	12 (33.3%)	10 (64.3%)	24 (70%)	12 (14.3%)
mean(SD)	21.5 (14.7)	20.6 (11.2)	22.7 (15.0)	18 (11.9)	20.7 (10.2)	26.2 (19.3)

Considerable data were missing for some patients; this is detailed in the “% miss” figure in brackets for each item

Table 2 Univariate analysis of patient factors associated with lack of benefit against each outcome

		Change in urgency episodes <= 20%			
	n	**Odds Ratio**	**Standard Error**	**95% CI**	**p-Value**
Characteristics					
Smoking status	107				
Non-smoker		Ref	Ref	Ref	Ref
Smoker		2.89	1.45	(1.08, 7.73)	0.034
constant		0.29	0.07	(0.17, 0.48)	<0.001
		Change in voiding frequency <= 10%			
Characteristics					
Age (centred)	110	1.04	0.02	(0.99,1.08)	0.104
constant		0.26	0.06	(0.17,0.42)	<0.001
Baseline voids	110	0.83	0.08	(0.68,1.00)	0.056
constant		2.36	2.58	(0.28,20.11)	0.432
IQol Score	110	1.02	0.01	(1.00,1.05)	0.048
constant		0.24	0.06	(0.15,0.41)	<0.001
		Incontinent at follow up			
Baseline leakage	104	1.17	0.07	(1.04,1.31)	0.007
constant		0.47	0.2	(0.21,1.07)	0.073
		Patient Global Impression of Improvement			
Age (centred)	108	1.04	0.02	(1.0,1.09)	0.055
constant		0.32	0.08	(0.21,0.51)	<0.001
BMI	108	1.07	0.04	(1.0,1.16)	0.056
constant		0.34	0.08	(0.22,0.54)	<0.001

Only significant associations are included
95% CI: 95% confidence interval

Table 3 Multivariate analysis of patient factors associated with lack of benefit against each outcome

		Change in voiding frequency <= 10%			
	N	**Odds Ratio**	**Standard Error**	**95% CI**	**p-Value**
Characteristics					
Age (centred)	110	1.03	0.02	(0.99,1.08)	0.172
Baseline voids		0.85	0.09	(0.69,1.04)	0.107
IQol Score		1.02	0.01	(1.00,1.04)	0.117
constant		1.61	1.88	(0.16,15.88)	0.685
		Patient Global Impression of Improvement			
Age (centred)	108	1.04	0.02	(1.0,1.09)	0.063
BMI		1.07	0.04	(1.0,1.16)	0.065
constant		0.32	0.08	(0.2,0.51)	<0.001