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The safety and efficacy of botulinum toxin-A in the management of bladder oversensitivity: A randomised double blind placebo controlled trial

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3 **The safety and efficacy of botulinum toxin-A in the management of bladder**
4 **oversensitivity: A randomised double blind placebo controlled trial**
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Abstract

Objective

To assess the safety and efficacy of botulinum toxin-A (botn-A) in the management of patients with Bladder oversensitivity (BO).

Patients and Methods

Twenty three consecutive patients with a diagnosis of BO refractory to anticholinergics were enrolled in this randomised, double blind, placebo controlled trial. Patients were randomly allocated to receive intra-detrusor injections of either botn-A (100U Botox®) or saline (placebo) via a flexible cystoscopic approach. The study was designed to have a 90% power to detect a change in the maximum cystometric capacity (MCC) of 30%. It was calculated that a total cohort of 58 patients would be required. Urodynamic assessment (UDS), voiding diaries (VD) and quality of life (QoL) were assessed at baseline and at 4 and 12 weeks following intervention.

Results

An interim analysis was performed and the trial halted after recruitment of 23 patients due to poorly perceived patient benefit. Data were analysed for 21 patients (10 botn-A; 11 placebo). In the treatment arm there was a significant increase in MCC (mean rise 105ml; $p=0.009$). However storage symptoms remained statistically unchanged following botn-A. Three patients in the treatment arm were required to perform clean intermittent self catheterisation with no clinical improvement. The limitations of this trial include the small samples size and the unplanned interim analysis.

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4 **Conclusions:** This is the first randomised, double blind, placebo controlled trial
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6 examining the effects of botn-A exclusively in patients with BO. A significant increase
7
8 in MCC was observed but this did not translate to clinical benefit with no change
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10 observed in the symptoms and quality of life for the majority of patients.
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17 **Trial registration:** ISRCTN no. 57577615

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20 (<http://www.controlled-trials.com/ISRCTN57577615/botulinum>)
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27 **What's known:** Numerous open label studies and several randomised controlled
28
29 trials have established that intra-detrusor injections of botulinum toxin A (botn-A) can
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31 produce dramatic symptomatic and quality of life improvement in patients with
32
33 detrusor overactivity (DO). Patients with bladder oversensitivity (BO) present with a
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35 similar symptom profile but are distinguished clinically by the absence of abnormal
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37 detrusor contractions. There are currently no randomised studies examining the
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39 effects of botn-A exclusively in patients with BO.
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51 **What's new:** This study examines the efficacy and safety of botn-A in patients with
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53 bladder oversensitivity. Although significant changes were observed in cystometric
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55 parameters, such as an increase in maximum cystometric capacity, there was no
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57 symptomatic improvement in 80% of patients.
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Introduction

Overactive Bladder Syndrome (OAB) is defined by the International Continence Society (ICS) as “Urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious pathology”[1]. First line management is usually undertaken in the primary care setting and consists initially of fluid management and bladder retraining followed by a trial of anticholinergic medication if required. If these efforts fail to control symptoms then a referral to secondary care usually follows where the patient will usually undergo further investigations including urodynamic assessment. At this stage a distinction can be made between patients with evidence of aberrant detrusor contractions during filling cystometry and those without. In the absence of any associated pathological abnormality the former condition is termed Idiopathic Detrusor Overactivity (IDO) and the latter as Bladder Oversensitivity (BO), previously termed motor urgency and sensory urgency respectively [2]. The most recent ICS terminology report defines bladder oversensitivity as “An increased perceived bladder sensation during filling with specific cystometric findings of i) early first desire to void ii) an early strong desire to void, which occurs at low bladder volumes iii) a low maximum cystometric capacity iv) no abnormal increases in detrusor pressure” [3]. In effect this divides patients with OAB into two distinct clinical groups. Both have the same symptomology i.e. frequency and urgency of micturition, but for one group this is correlated with an abnormal contraction of the bladder (IDO), whereas in the other it is not (BO).

Botulinum toxin-A (botn-A) has emerged as an effective second line therapy in the management of OAB and detrusor overactivity (DO) with a recent European consensus giving it a grade A recommendation for use in this condition [4].

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3 Whist there is some experience of managing BO patients with botn-A reported in the
4 literature they tend to form part of larger heterogeneous patient cohorts. To date
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6 there have been no randomised, placebo controlled trials specifically examining the
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8 effects of botn-A in this group of patients.
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For Peer Review Only

Materials & Methods

This study was a randomised, double blind placebo controlled trial conducted at a single centre. The trial was performed in line with Good Clinical Practice and had local ethical approval (registration no. 06/Q0704; ISRCTN no. 57577615). Patients were randomised to either 100U Botox® (Allergan, Irvine, California) or normal saline (placebo). A list was prepared by an independent statistician and held in the trials office of the pharmacy department. Eligible patients were assigned a study number in sequence and the pharmacy dispensed either the placebo or active treatment according to the list. The trial injections were collected and prepared by a trained nurse who had no contact with the patient, such that the investigators received 10ml of clear solution without knowing whether it contained 100U of Botox or placebo.

Patients (18-79y) who fulfilled the criteria for a diagnosis of BO, as defined in the introduction, were invited to participate in the trial. All patients had failed conservative and pharmacological therapy with at least one anticholinergic medication. Exclusion criteria included current or planned pregnancy, breast feeding, painful bladder syndrome, pre-existing neurological condition, evidence of bladder outflow obstruction, indwelling catheter, previous bladder surgery, previous urological use of botn-A and continued anticoagulation with heparin or warfarin.

Urodynamic data were collected at weeks 0 and 12. These specifically included maximum cystometric capacity (MCC), first desire to void (FD), normal desire to void (ND), post void residual volume (PVR) and the presence/absence of DO. At week 0, 4 and 12, patients completed a three day voiding diary which recorded 24hr urinary frequency (UF), urinary urgency (UU) and urge urinary incontinence (UUI). They

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3 were also asked to complete the short forms of the Urogenital Distress Inventory
4 (UDI-6) and Incontinence Impact Questionnaire (IIQ-7) and the Patient Perception of
5 Bladder Condition questionnaire (PPBC) to obtain a patient orientated assessment of
6 the treatment.
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13 The primary endpoint of the study was a change in MCC. A sample size of 58 was
14 calculated to achieve a 90% power to detect a difference of 30%. Secondary
15 endpoints included other urodynamic parameters [first desire to void (FD), normal
16 desire to void (ND), post void residual volume (PVR)], OAB symptoms, assessment
17 of QoL and PPBC.
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26 The study procedures were performed in the out-patient setting by a single surgeon.
27 Urodynamics were performed in accordance with the ICS guidelines [5]. Prior to any
28 intervention all patients gave a urine sample to exclude infection (and pregnancy if
29 appropriate) and all received a oral dose of ciprofloxacin 500mg. Lignocaine gel
30 (Instillagel®, Clinimed, UK) was applied to the urethra prior to cystoscopy. Intra-
31 detrusor, trigone sparing injections of either 100 U botn-A (Botox®, Allergan) or
32 normal saline (placebo) were performed with a flexible cystoscopic technique using a
33 4mm Olympus needle. Ten sites along the base, posterior and lateral walls of the
34 bladder were injected with 1ml of solution containing either 10 U botn-A (Botox®,
35 Allergan) in normal saline or normal saline alone (placebo). Three small bladder
36 biopsies were taken, from 1cm above and lateral to the left ureteric orifice, baseline
37 and at week 12 for use in a separate study. All patients were given a three day
38 course of ciprofloxacin 500mg twice daily. Patients were individually unblinded after
39 12 weeks once all study data had been collected. Those who had received placebo
40 were offered 100U Botox in an open label fashion.
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Independent statistical advice was sought with regards data. A repeated measures generalised linear model was used to compare the pre- and post intervention variable outcomes using SPSS® v17.0.

Results

Between November 2007 and November 2009 a total of 28 patients were identified with a diagnosis of BO and invited to participate in this trial. Five patients declined with concerns regarding the risk of having to perform CISC. Of the 23 patients who were injected as per protocol – 1 failed to attend follow up and 1 was re-diagnosed as interstitial cystitis (Consort diagram – figure 1). Complete data for 21 patients was available (treatment arm = 10, placebo = 11. At this stage an unplanned interim analysis was undertaken with advice from the local research governance board, due to concern that the majority of patients had reported no clinical benefit. Following data analysis it was determined that there was likely to be little benefit in continued recruitment and the trial was terminated.

Table 1 describes the baseline urodynamic parameters and OAB symptoms for the entire cohort and demonstrates a low MCC, FD and ND in addition to a high day time UF which is associated with UU on over 70% of occasions. The average age of the botn-A and placebo groups was not significantly different (49.6+/-19 and 46.7+/-17y, p=0.7). The ratio of males to females was 2:8 and 4:7 in the botn-A and placebo group respectively.

Urodynamic variables: There was a significant rise in MCC, (the primary endpoint of the study), in patients receiving botn-A compared to placebo (p=0.009) (figure 2). In the botn-A arm there was an mean increase in FD (figure 3), ND and PVR although

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3 they did not achieve statistical significance. One patient in the treatment arm and two
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5 in the placebo arm demonstrated DO at week 12 which had not been observed at
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7 baseline.
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11 *OAB Symptoms:* Overall there was no significant difference observed in UF, UU or
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13 UUI at any time point in either group, and no trends were noted (figures 4–6).
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15 Individually, only two patients felt their symptoms were improved by the injections,
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17 whilst for the remainder their symptoms scores remained unchanged.
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21 *QoL measures:* There was significant improvement in IIQ-7 at 4 weeks which
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23 became non-significant by week 12. There was no significant improvement in UDI-6
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25 at any stage.
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29 *Patient perception of bladder condition:* No significant change was observed in
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31 PPBC score throughout the study period.
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35 These results are summarised in Table 2.
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39 *Adverse events:* Three patients in the botn-A group were required to perform CISC
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41 and none of them reported any symptomatic improvement. No one in the placebo
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43 group required CISC. UTI was detected in 4 patients in the botn-A arm (2 associated
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45 with performing CISC) and 1 in the placebo arm.
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49 A patient in the botn-A group reported a general malaise which lasted two months
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51 following injections with no obvious cause identified. The patient did not require any
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53 specific intervention.
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Discussion

This study is the first randomised controlled trial examining the effects of botn-A exclusively in patients with BO. Despite enrolling only a third of the patients suggested by the power calculation the primary endpoint was achieved with the data demonstrating a significant increase in MCC and a trend towards improvement in FD and ND. This did not, however, translate into a meaningful clinical benefit as there was no overall difference detected in OAB symptoms, QoL (with the exception of IIQ-7 at week 4) or PPBC. Individually, only two (20%) patients in the treatment arm derived any benefit from the injections, whilst the remainder experienced no change in their symptoms.

Several studies include patients with BO in their cohorts. Schulte-Baukloh et al. reported a series of seven patients, who received 300U botn-A. At 12 weeks they observed a significant rise in MCC and FD with a decrease in UF, nocturia and pad usage[6]. Cohen et al reported a randomised controlled trial comparing 100u and 150U of botn-A in a cohort including patients with BO or IDO, although the authors do not distinguish between them in their analysis. Instead patients were sub-divided into those with UUI (“wet”) and those with no UUI (“dry”). They found a significant decrease in UF in the “dry” group and a significant decrease in UUI in the “wet” group. They found no significant change in MCC or PVR and they did not observe any significant difference between the two doses [7]. Flynn et al. also found no significant change in MCC and UF in a trial which compared either 200u or 300u botn-A with placebo in a group of patients with BO and IDO. They found significant improvement in UUI and QoL measures[8]. In an open label study Schmid et al described significant improvement in 100 patients with OAB (46 BO and 54 IDO)

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3 who received 100u of botn-A. They observed an overall reduction in UF and UU.
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5 They did not find a difference in treatment response between those with BO and
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7 those with IDO [9]. A recent randomised, placebo controlled, dose response trial
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9 involving 313 patients demonstrated an improvement in symptoms and QOL
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11 measures overall. This study concluded that the presence of DO during filling
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13 cystometry did not influence outcome, although the study was not specifically
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15 designed to examine BO [10]. Overall these studies tend to demonstrate some
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17 clinical improvement, although the data are inconsistent, particularly with regards to
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19 changes in MCC and UF.
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26 Two studies examining only patients with IDO demonstrate more consistent positive
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28 results. Sahai et al found an improvement in almost all variables studied at 4 and 12
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30 weeks after 200u botox with reductions in UF (15.4 to 9.2), UU (11.7 to 3.6) and UUI
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32 (5.0 to 1.5) and an increase in MCC (181 to 313) at 12 weeks[11]. Khan et al found
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34 UF, UU & UUI reduced significantly by 67%, 100% and 54% respectively at 4
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36 weeks[12]. In these studies dramatic improvements are observed in the symptoms of
37
38 the majority of patients. In this study only 20% of patients demonstrated a
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40 symptomatic improvement with no change (or trend towards change) in UF, UU and
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42 UUI in the remaining 80%. We observed a significant increase in MCC (primary
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44 endpoint) which did not correlate with a symptomatic improvement. On that basis we
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46 sought statistical advice on re-powering the study to a symptomatic endpoint but
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48 interim power calculations (Statmate™ Graphpad Software) suggested that even
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50 with the small number of patients recruited we should have been able to detect a
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52 significant difference of 4, 3 and 1.6 episodes per 24 hours for UF, UU and UUI.
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59 Possible explanations for the observed lack of effect include insufficient dosage,
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although many of the studies above utilised 100U of Botn-A with positive

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3 symptomatic outcomes. A further possibility is injection technique. The goal in DO is
4 to inject all areas of the bladder to “knock out” aberrant detrusor contractions. In true
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6 BO no DO exists and it is therefore possible that localised injections into the bladder
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8 base and trigone might be more appropriate, as this area contains the most dense
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10 sensory innervation in the bladder and injections here have been shown to be
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12 beneficial in non-neurogenic OAB [13]. Furthermore trigonal injections have now
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14 been shown not to induce vesico-ureteric reflux, an early potential concern with this
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16 technique [14;15]
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23 In addition to an established motor effect botn-A has been shown in a number of
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25 human studies to have a modulatory effect on the sensory apparatus of the bladder.
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27 This includes inducing a decreased expression of the purinergic receptor P2X3, the
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29 vanilloid receptor TRPV1, prostaglandins and nerve growth factor [16-18], all of
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31 which have been implicated in the pathogenesis of IDO and BO [19-21]. These
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33 observations, however, could be a secondary effect due to reduction in bladder
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35 contraction/pressure rather than due to primary action of the toxin. More direct
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37 evidence of sensory modulation has been derived from animal models in which
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39 decreased release of the neurokinins, CGRP and SP, (which have also been
40
41 implicated in the pathogenesis of OAB), were observed following intra-vesical
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43 instillation of botn-A [22-24]. Caution must be exercised when extrapolating these
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45 results to IDO or BO as these laboratory models do not reproduce the specific
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47 pathophysiology, which to date, remains unclear.
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54 It remains to be seen whether BO and IDO represent distinct pathological entities.
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56 Haylen et al. prospectively compared 77 patients with BO with 74 patients with IDO
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58 and could find no significant clinical differences between the 2 groups except for a
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60 significantly increased incidence of UUI in the IDO group [25]. A distinction has been

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3 described at the molecular level, by Lui et al. who analysed bladder biopsies from
4 patients diagnosed with IDO or BO. They found trigonal TRPV-1 in BO patients to be
5 higher than that of the bladder body mucosa or that of control tissue. In contrast no
6 differences were found in TRPV-1 levels from the trigone or bladder base in IDO
7 patients [26].
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16 Currently the diagnosis of BO depends on the absence of aberrant detrusor
17 contractions during filling cystometry but this can be unreliable, lacking in
18 reproducibility and there will undoubtedly be some overlap with IDO [27;28]. A
19 cystometric distinction between the IDO and BO is unlikely to influence or provide
20 any useful prediction of response to first line treatments [29;30]. In this study it's
21 possible that these cystometric limitations have resulted in patients with IDO rather
22 than BO being recruited, but given the positive outcomes for patients with IDO (as
23 discussed above) we would have expected this to improve the overall symptomatic
24 results. Despite these reservations the distinction between BO and IDO is important
25 for future research and may be clinically relevant when counselling patients before
26 botn-A as our data suggests the likelihood of a satisfactory outcome will not be as
27 good for BO.
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45 Although the primary endpoint was achieved with a clear and significant increase in
46 MCC, it did not correlate with an improvement in patient symptoms. This primary end
47 point was chosen during the design phase as it was felt to be relatively objective and
48 that previous experience with IDO patients had shown association between a rise in
49 MCC and symptomatic improvement [11]. In retrospect, using a symptom as the
50 primary endpoint, for example UU, would have been more appropriate.
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3 The authors accept that this data is limited by the small numbers of patients and the
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5 unplanned interim analysis. Nevertheless the lack of any symptomatic improvement
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7 in most patients in this study, despite the changes in their urodynamic parameters is
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9 significant and raises questions regarding the role of botn-A as a therapy for this
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11 specific sub-group of OAB, particularly as we are used to observing far more
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13 dramatic symptomatic improvements in the majority of patients in the IDO
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15 population. In a wider sense this study also highlights the need for continued
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17 research to attempt to understand and distinguish what distinct pathological entities
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19 OAB represents and to describe their specific aetiologies so that future therapies can
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21 be targeted more effectively.
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30 **Conclusion**

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33 The results of this double blind placebo controlled trial in the use of botn-A in BO are
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35 disappointing. Despite demonstrating a significant increase in MCC there was no
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37 overall improvement in OAB symptoms orl QoL. No clinical benefit was observed in
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39 80% of patients reinforcing the need for continued research to identify and define the
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41 different pathophysiological processes which present as the OAB syndrome.
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For Peer Review Only

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5 Figure 1:- Consort Flowchart
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9 Figure 2: - Maximum cystometric capacity (MCC) at baseline and at 12 weeks following intra-
10 detrusor injections. There is a significant rise in the MCC in the botn-A group ($p=0.009$). No change is
11 observed in the placebo arm.
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16 statistical significance.
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21 Figure 4: - Episodes of urinary frequency at weeks 0, 4 & 12. No significant differences were detected
22 and no trends were evident.
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27 Figure 5:-Episodes of urinary urge at weeks 0, 4 & 12. No significant differences were detected and
28 no trends were evident.
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33 Figure 6: - Episodes of urge urinary incontinence at weeks 0, 4 & 12. There is no significant difference
34 detected and no trends observed.
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Table 1 – Baseline cystometric and symptom scores for entire study cohort

	Mean	SD
MCC	275.2 ml	70.6
FD	98.4 ml	64.6
ND	146.0 ml	56.8
PVR	22.1 ml	25.2
UF	14.2 voids/24hrs	4.4
UU	11.6 voids/24hrs	5.9
UUI	1.7 voids/24hrs	2.2

MCC – maximum cystometric capacity; FD – first desire to void; ND – normal desire to void; PVR – post void residual volume; UF – urinary frequency; UU – urinary urgency; UUI – Urge urinary incontinence.

Table 2 – Comparison of the botn-A and placebo arms at baseline (BL) and 4 and/or 12 weeks

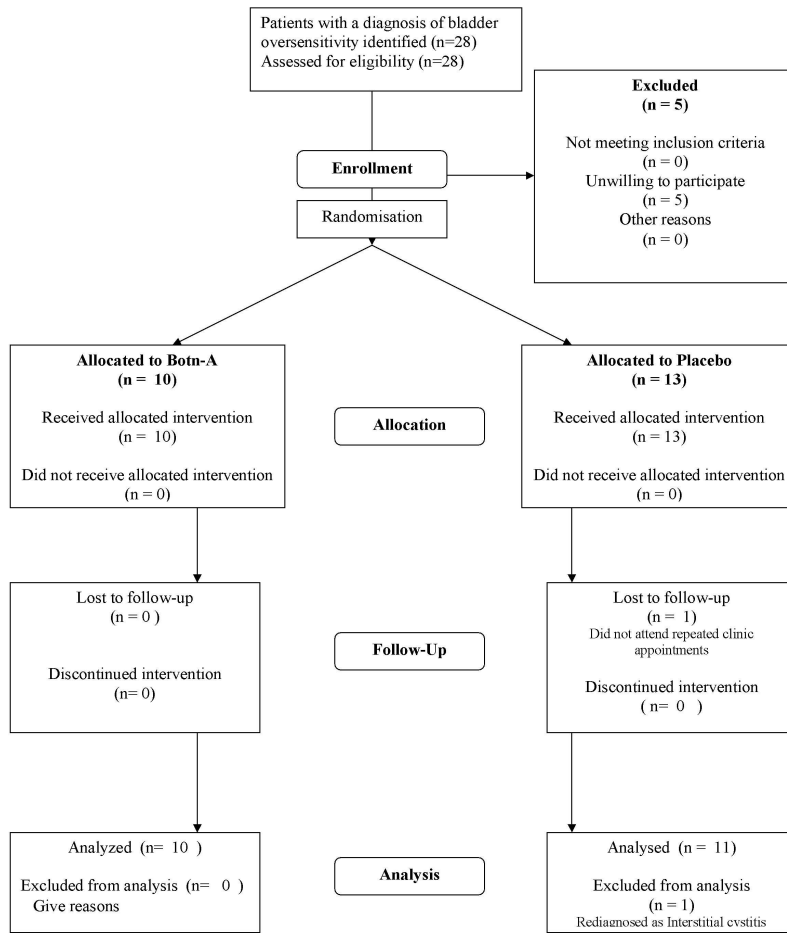
		Botn-A	Placebo		Difference between mean change (95% CI)	p
MCC	BL	259	290			0.33
	12	365	290		105 (30 - 180)	0.009
FD	BL	86	110			0.40
	12	149	108		65 (-41 to 172)	0.22
ND	BL	119	171			0.03
	12	189	177		69 (-40 to 168)	0.22
PVR	BL	21	23			0.82
	4	62	29		35 (-24 to 95)	
	12	78	30		50 (-20 to 120)	0.22
UF	BL	15.6	12.8			0.17
	4	14.7	12.1		-0.1 (-3.9 to 3.7)	
	12	14.9	12.8		-0.9 (-4.9 to 3.1)	0.82
UU	BL	12.4	10.8			0.57
	4	12.8	11.0		-0.9 (-4.0 to 4.4)	
	12	12.5	11.8		-1.1 (-5.0 to 2.8)	0.78
UUI	BL	1.2	2			0.38
	4	1.4	2.4		-0.1 (-2.5 to 2.2)	
	12	1.1	2.9		-1.0 (-3.7 to 1.7)	0.52
IIQ-7	BL	19.2	12.9			0.04

	4	12.7	13.9		-7.3 (-13 to -1.0)	
	12	14.2	15.2		-5.1 (-11 to 1.5)	0.06
UDI-6	BL	10.3	8.3			0.40
	4	9.2	8.9		-2.0 (-4.9 to 1.0)	
	12	8.2	8.6		-1.2 (-6.1 to 3.7)	0.50
PPBC	BL	3.6	3.9			0.33
	4	3.4	3.7		0 (-0.7 to 0.6)	
	12	3.7	3.8		0.2 (-0.6 to 1.0)	0.58

Botn-A – botulinum toxin-A; MCC – maximum cystometric capacity; FD – first desire to void; ND – normal desire to void; PVR – post void residual volume; UF – urinary frequency; UU – urinary urgency; UUI – Urge urinary incontinence. IIQ-7 – Incontinence impact questionnaire short form; UDI-6 – Urogenital distress inventory short form; PPBC – Patient perception of bladder condition.

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Figure 1 - Consort Flowchart



209x297mm (300 x 300 DPI)

Figure 2

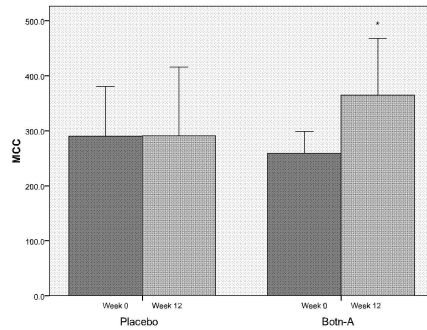


Figure 2: - Maximum cystometric capacity (MCC) at baseline and at 12 weeks following intra-detrusor injections. There is a significant rise in the MCC in the botn-A group ($p=0.009$). No change is observed in the placebo arm.
209x297mm (300 x 300 DPI)

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Figure 3

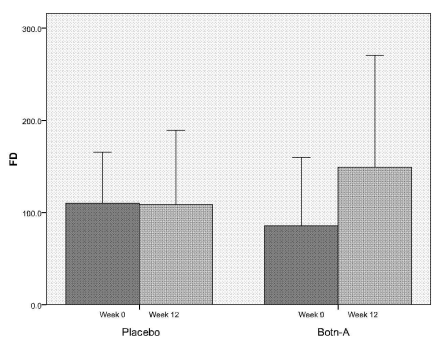


Figure 3: - First desire to void. An increase is observed in the botn-A arm although it does not reach statistical significance.
209x297mm (300 x 300 DPI)

Figure 4

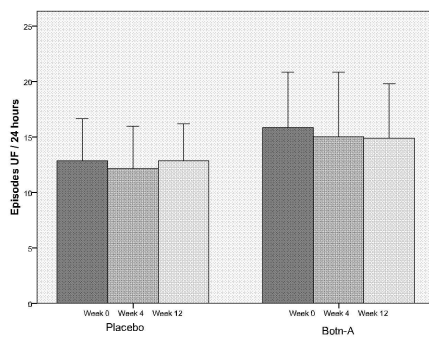


Figure 4: - Episodes of urinary frequency at weeks 0, 4 & 12. No significant differences were detected and no trends were evident.
209x297mm (300 x 300 DPI)

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Figure 5

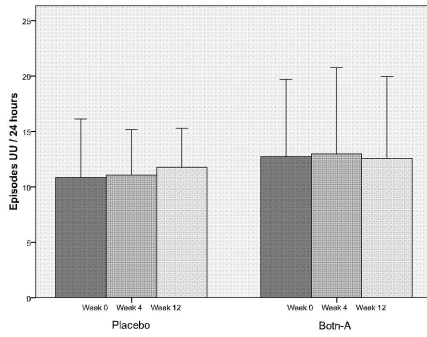


Figure 5:-Episodes of urinary urge at weeks 0, 4 & 12. No significant differences were detected and no trends were evident.
209x297mm (300 x 300 DPI)

Figure 6

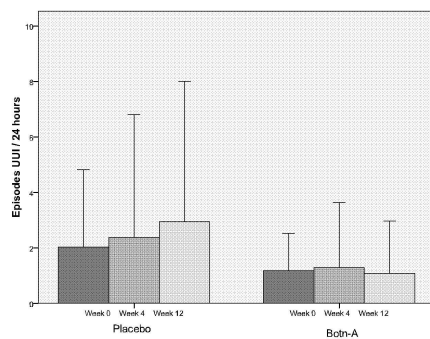


Figure 6: - Episodes of urge urinary incontinence at weeks 0, 4 & 12. There is no significant difference detected and no trends observed.
209x297mm (300 x 300 DPI)