Research Paper

Multiple Sclerosis

Multiple Sclerosis
16(11) 1349–1359

DOI: 10.1177/1352458510378020
msj.sagepub.com
SAGE

Randomized controlled trial of Sativex to treat detrusor overactivity in multiple sclerosis

RBC Kavia[1], D De Ridder[2], CS Constantinescu[3], CG Stott[4] and CJ Fowler[1]

Abstract

Background: Bladder dysfunction is a common feature of multiple sclerosis (MS).

Objective: In this study we aimed to assess the efficacy, tolerability and safety of Sativex® (nabiximols) as an add-on therapy in alleviating bladder symptoms in patients with MS.

Methods: We undertook a 10-week, double-blind, randomized, placebo-controlled, parallel-group trial in 135 randomized subjects with MS and overactive bladder (OAB).

Results: The primary endpoint was the reduction in daily number of urinary incontinence episodes from baseline to end of treatment (8 weeks). Other endpoints included incidence of nocturia and urgency, overall bladder condition (OBC), daytime frequency, Incontinence Quality of Life (I-QOL), Patient's Global Impression of Change (PGIC) and volume voided. The primary endpoint showed little difference between Sativex and placebo. Four out of seven secondary endpoints were significantly in favour of Sativex: number of episodes of nocturia (adjusted mean difference −0.28, $p = 0.010$), OBC (−1.16, $p = 0.001$), number of voids/day (−0.85, $p = 0.001$) and PGIC ($p = 0.005$). Of the other endpoints, number of daytime voids was statistically significantly in favour of Sativex (−0.57, $p = 0.044$). The improvement in I-QOL was in favour of Sativex but did not reach statistical significance.

Conclusions: Although the primary endpoint did not reach statistical significance, we conclude that Sativex did have some impact on the symptoms of overactive bladder in patients with MS, providing evidence of some improvement in symptoms associated with bladder dysfunction in these subjects.

Keywords

cannabinoid, detrusor overactivity, multiple sclerosis, overactive bladder, Sativex

Date received: 9th October 2009; revised: 19th March 2010; 15th June 2010; accepted: 16th June 2010

Introduction

Overactive bladder (OAB) was defined in 2002 by the International Continence Society as a condition characterized by urgency, with or without urge incontinence, usually with high void frequency and nocturia, in the absence of local pathological or hormonal factors.[1] The majority of multiple sclerosis (MS) sufferers (90%) develop lower urinary tract signs within 10 years of contracting the disease,[2] most commonly OAB. Symptoms of OAB such as episodes of leakage, increased frequency and urgency disrupt patients' daily routine, and reduce quality of life.[3]

Cannabis-containing medicines were almost certainly used in ancient times for female genito-urinary disorders.[4] Their use then lapsed, to enjoy a renaissance in the nineteenth century as a 'regulator of the catamenial function', for the treatment of a variety of pain syndromes, in particular of neuralgic origin, as an antispasmodic, and in the treatment of dysuria.[4,5] As recently as 1971 tincture of cannabis was prescribed by British doctors,[6] but since then it has not been available legally for medicinal use. However, thousands of patients continue to use cannabis for conditions such as AIDS, MS and chronic pain.[7]

[1]National Hospital for Neurology and Neurosurgery, London, UK.
[2]Universitaire Ziekenhuizen Leuven, Leuven, Belgium.
[3]Queen's Medical Centre, Nottingham, UK.
[4]GW Pharmaceuticals Ltd, Salisbury, UK.

Corresponding author:
Professor Clare J Fowler, Department of Uro-Neurology, Box 71, National Hospital for Neurology and Neurosurgery, Queen Square, London, WC1N 3BG, UK
Email: c.fowler@ion.ucl.ac.uk

The scientific basis for the effect of cannabis on the uterus and bladder lies with the fact that these organs express CB_1 receptors. The effect of cannabis agonists, such as delta-9-tetrahydrocannabinol (THC), in the rodent experimental model is complex; in the inflamed rodent bladder, cannabinoid receptor agonists significantly increase the micturition threshold,[8–10] predominantly through a CB_1 receptor effect. Isolated tissue studies have shown both relaxation and contraction effects on bladder strips which may be mediated by THC at transient receptor potential vanilloid 1 ($TRPV_1$) receptors, resulting in the release of calcitonin-gene related peptide.[11] Cannabidiol (CBD) appears to have an antihyperalgesic action that is also mediated by $TRPV_1$ receptors.[12] The interaction between $TRPV_1$ and cannabinoid receptors is as yet undetermined, although the endogenous cannabinoid arachidonoylethanolamide (anandamide; AEA) is known to act at both. The bladder is rich in $TRPV_1$ receptors and these are increased in conditions of inflammation and OAB, particularly in neurogenic cases.[13] There may also be an effect at central nervous system (CNS) receptors, since CB_1 receptors have also been demonstrated in the vicinity of the periaqueductal grey, pons, hypothalamus and basal ganglia, as well as the lumbar spinal cord of the rat,[14] all regions known to be involved in bladder control. The use of CBD, which does not bind to CB_1 when given alongside THC, has been shown to reduce the possible adverse effects seen when subjects are dosed with THC alone.[15] CBD is also reported to have beneficial neuroprotective and anti-oxidant activity.[16,17]

A survey of 112 patients with MS who used 'street' cannabis reported improvements in urgency (64%), urgency incontinence (55%), and hesitancy (59%),[18] providing the rationale for a small open-label pilot study of the effect of Sativex in subjects with advanced MS.[2] Sativex was found to improve several MS-related urinary symptoms, with decreases in frequency, nocturia, incontinence, and urgency episodes and increases in the proportion of voids that were 'planned', or occurred with a normal desire to void. Side effects were few and good tolerability was observed. These results were considered sufficiently encouraging to warrant this multi-centre, randomized, double-blind, placebo-controlled clinical study designed to evaluate the efficacy, safety and tolerability of Sativex in subjects with OAB due to MS.

Methods

Study subjects

Adults with a diagnosis of MS with symptoms of OAB who had failed to respond adequately to first-line therapies, principally anticholinergics, were invited to participate in this 10-week, placebo-controlled study. Subjects at 15 centres (nine in the UK, three in Belgium and three in Romania) were screened to determine eligibility. Subjects were required to be on a stable dose of anticholinergic medication for at least 14 days prior to study entry which remained unchanged throughout the study, and to have had at least three incontinence episodes over five consecutive days during the baseline period, as assessed by a self-report voiding diary, completed daily.

Exclusion criteria included (i) the presence of symptomatic urinary tract infection or any other known cause for detrusor overactivity; (ii) performing intermittent self-catheterization; (iii) history of use of cannabis or cannabis-derived medicines (street cannabis, dronabinol or nabilone) within 7 days of study entry; (iv) hypersensitivity to cannabinoids or any of the excipients of the medication; (v) a history of major psychiatric disorder (other than depression associated with underlying condition); (vi) severe personality disorder or history of alcohol or substance abuse; (vii) severe cardiovascular disorder, history of epilepsy or significant renal or hepatic impairment; and (viii) concomitant use of fentanyl, levodopa, or sildenafil citrate. The study was conducted in accordance with the principles of the Declaration of Helsinki and ICH Good Clinical Practice. Eligible subjects gave written consent and the study protocol (dated 5 June 2002) was approved by the Research Ethics Committees appropriate to each investigator (12 in total).

Study medication

Sativex (nabiximols), an endocannabinoid system modulator, is produced by GW Pharma Ltd. It is derived from strains of *Cannabis sativa* L. plants developed to produce high and reproducible yields of a principal cannabinoid, in this case THC or CBD. Extraction of these Botanical Raw Materials produces Botanical Drug Substances (BDS) (extracts) which contain a principal cannabinoid, minor amounts of other cannabinoids and terpenes, are blended and then formulated in a solution containing ethanol, propylene glycol and peppermint oil flavouring to produce Sativex. It was administered as a pump-action oromucosal spray, each 100 µl actuation of the formulated THC BDS:CBD BDS delivering a dose of 2.7 mg THC and 2.5 mg CBD, and each actuation of placebo delivering excipients plus colorants and flavouring. The maximum permitted dose of study medication was eight actuations in any 3-h period, and 48 actuations in any 24-h period. Subjects self-titrated to their optimal dose, based on efficacy, tolerability and the maximum permitted dose, and were instructed not to increase their total daily number of sprays by more than 50% of the

previous day's dose. If intoxication was experienced at any time then either the next scheduled dose was omitted and/or the number of sprays per dose was reduced. Subjects recorded the time and number of actuations in their daily diaries each time they self-medicated, and the investigator was responsible for reconciling this diary data with the number of used and unused vials of study medication returned at each scheduled visit.

Study design

Eligible subjects entered a 2-week baseline period during which they kept a daily diary of their urinary function. At Visit 2, if still eligible, they were randomized to either an active or to a placebo group, using a pre-determined randomization code in which treatment allocation was made using permuted blocks of four (see Figure 1). The study medication was provided in glass vials labelled with the GW name, study code, subject number, visit number and expiry date. As Sativex is a plant-based extract with a distinctive smell, taste and colour, both it and the placebo contained peppermint oil to blind the smell and taste, and the placebo also contained colorants to match the colour of the plant extract. The identity of the study medication was contained in individually sealed envelopes sent to each centre, which could be opened only in the case of a medical emergency where knowledge of which study medication the subject had received would affect the course of treatment.

Study medication titration was introduced gradually at Visit 2 and the subject was observed for 4 h for any signs of intoxication, which were recorded on a 0–10 Numerical Rating Scale (NRS) (0 = No intoxication, 10 = Extreme intoxication). Subjects who satisfactorily completed initial dosing were instructed to continue titration over the next 2 weeks. No specific target dose was set. If intoxication was experienced subjects were advised to reduce or omit a dose. Visits 3 and 4 were telephone contacts after 2 and 5 weeks of treatment, respectively, to review titration, compliance and Adverse Events (AEs). Visit 5 was conducted at the end of treatment (week 8) or on withdrawal.

Physical examination, haematological and biochemical tests, and an electrocardiogram were performed at baseline and at the withdrawal/completion visit. Subjects completed a daily diary for the duration of the study, recording the time and number of doses of study medication taken, the time and frequency of incontinence episodes, micturition, feelings of urgency, nocturia and number of incontinence pads used. In addition, incontinence pad weight and daily voided volume data were collected for 3 days per week during baseline and weeks 7 and 8. The efficacy questionnaires consisted of the Incontinence Quality of Life (I-QOL),[19] a 0–10 NRS of their Overall Bladder

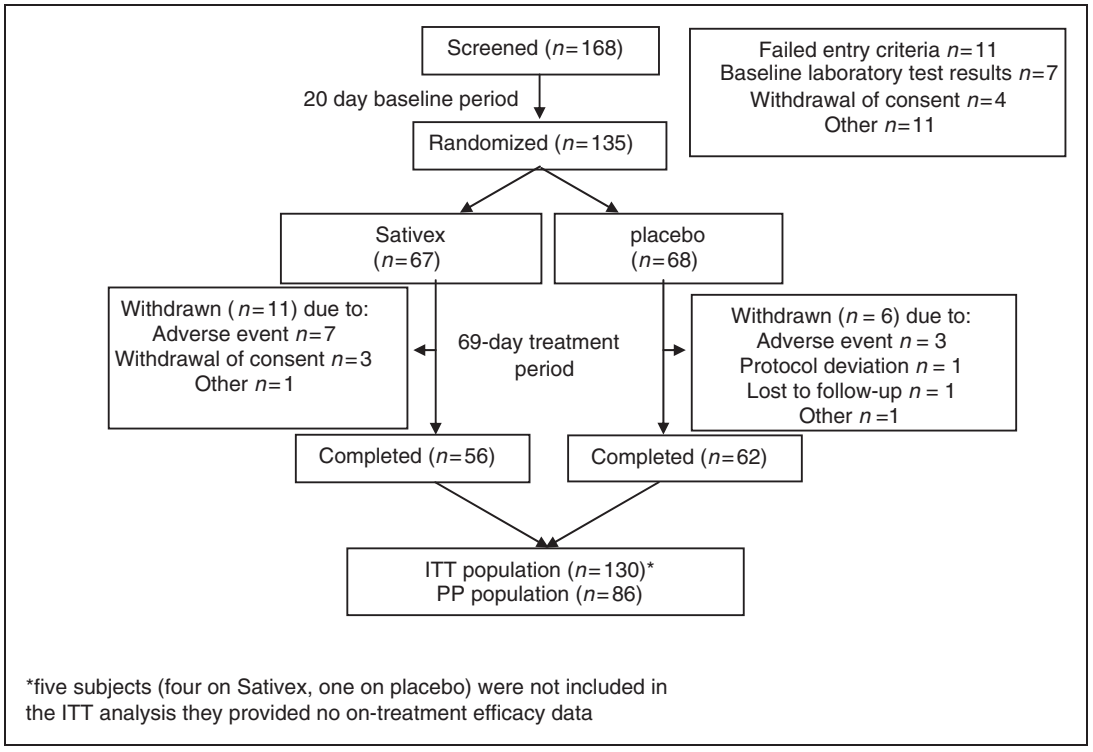


Figure 1. Disposition of subjects. ITT, indent to treat; PP, per protocol.

Condition (OBC) (0 = no problems to 10 = intolerable problems), and the Patient Global Impression of Change (PGIC). Details of AEs were recorded throughout the study. Subjects who completed the trial were offered the opportunity to participate in an open-label extension study.

At one study centre standard voiding cystometry was performed pre- and post-treatment using a 6 French urethral catheter and a 6 French rectal catheter with the fluid perfusion system on the Dantec Suite (Medtronic). All subjects were assessed in the sitting position. Three centres measured post-micturition residual volumes during the baseline period.

Statistical analysis

Primary endpoint. The primary measure of efficacy was the change in the number of incontinence episodes from baseline to end of treatment. End of treatment was defined as the last available data from weeks 7–8. If the subjects withdrew prior to this period, then end of treatment was considered at either week 3 or week 5.

The sample size was based on the primary variable of number of incontinence episodes. The sample size calculation from a previous open-label trial using the same medication suggested an estimated standard deviation for change from baseline in number of incontinence episodes/24 hours of 0–90. Using a two-sided hypothesis test at the 5% level, it was estimated that, allowing for dropouts, 130 subjects commencing treatment would be sufficient to provide 104 evaluable subjects (52 each arm) to detect a difference between treatments of 0.5 episodes of incontinence per 24 h at 80% power.

The intention to treat (ITT) and per protocol (PP) populations were used for all efficacy analyses (see Figure 1). The ITT population was defined as all subjects who entered the study and were randomized and received at least one dose of medication.

The primary endpoint of incontinence episode frequency was summarized by treatment group for baseline, weeks 3 and 5 on medication, or end of treatment. Change in frequency was compared between treatment groups using analysis of covariance (ANCOVA). The model included treatment and centre as factors, and baseline incontinence episode frequency score as a covariate. The primary analysis was based on the ITT population.

A post-hoc exploratory analysis of 49 subjects who were recruited at specialist urology centres and with data of post-micturition residual volumes enabled an ANCOVA of the primary endpoint to be undertaken, with post micturition volume and gender as covariates.

Secondary endpoints. Void urgency and nocturia episodes, the number of incontinence pads used per day, the change in symptoms measured on a 0–10 NRS of OBC, voided urine volume, the frequency of daytime voids and incontinence pad weight were summarized and analysed in the same manner as the primary efficacy endpoint. No allowance for multiplicity (multiple statistical analyses) was made.

A responder analysis of the frequency of urgency episodes was provided for those subjects reporting urgency at baseline. Responders were identified as those who at the end of treatment were not experiencing void urgency, and non-responders as those who continued to experience void urgency episodes. The results were presented by treatment group, and the percentage of responders was compared between groups using Fisher's exact test.

The I-QOL scale comprises 22 items assessing the impact of lower urinary tract symptoms on quality of life, each with a five-point response scale: 1 = Extremely, 2 = Quite a bit, 3 = Moderately, 4 = A little, 5 = Not at all. A higher score represented a better quality-of-life rating. The responses to each of the 22 items were summed and averaged for a total score and then transformed to a 0–100 scale for ease of interpretation. Descriptive statistics were provided for the total I-QOL and the three subscale scores (avoidance and limiting behaviour, psychosocial impacts, and social embarrassment). The total transformed I-QOL scores were analysed and summarized in the same manner as for the primary endpoint.

For the PGIC scale, subjects were asked at Visit 5 (on completion or withdrawal) to give their impression of the overall change in their condition since entry into the study using a seven-point scale; comparison between treatment groups was performed using Fisher's exact test.

Results

Study population

Recruitment took place between January 2003 and December 2004 with 168 subjects entering the baseline phase. Of these, 33 were excluded at screening, resulting in 135 subjects randomized, 67 to Sativex and 68 to placebo (Figure 1). Table 1 provides details of demographics of subjects enrolled into this study.

Of the 135 subjects who started the study, 17 (12.6%) withdrew (11 on the active treatment and six on placebo); 56 (83.6%) subjects completed the study in the Sativex arm and 62 (91.2%) in the placebo arm. Further details are summarized in Figure 1.

Five subjects were excluded from the ITT population (four from the active treatment group and one from the placebo group) because they did not provide any 'on-treatment' efficacy data. The PP population

Table 1. Baseline demographic details

		Number of subjects (%)		
		Sativex ($n=67$)	Placebo ($n=68$)	Total ($n=135$)
Gender	Male	15 (22.4)	22 (32.4)	37 (27.4)
	Female	52 (77.6)	46 (67.6)	98 (72.6)
Ethnic Origin	Caucasian	64 (95.5)	64 (94.1)	128 (94.8)
	Asian	2 (3.0)	3 (4.4)	5 (3.7)
	Black	0	1 (1.5)	1 (0.7)
	Other*	1 (1.5)	0	1 (0.7)
Previous Cannabis Use		21 (31.3)	27 (39.7)	48 (35.6)
			Mean (SD)	
Age (years)		48.6 (9.3)	46.8 (11.2)	47.7 (10.3)
Weight – Female (kg)		69.2 (17.3)	70.8 (12.3)	70.0 (15.2)
Weight – Male (kg)		75.4 (15.1)	77.2 (7.4)	76.5 (11.0)
Episodes of Incontinence/day		1.8 ($n=63$)	2.1 ($n=66$)	
Episodes of Nocturia/day		1.6 ($n=63$)	1.5 ($n=66$)	

*Subject was a Turkish Cypriot female.

comprised 42 subjects in the active medication group and 44 in the placebo group; reasons for exclusions of these 46 subjects are listed in Table 2. This high proportion of exclusions illustrates the difficulty in maintaining subject compliance with the study protocol.

Dosing

Subjects on placebo tended to take higher daily doses of study medication than those on Sativex: Sativex subjects took a mean of 8.91 actuations (median 7.19) compared with placebo subjects who took a mean of 17.05 actuations (median 14.22).

Efficacy measures

The primary endpoint of reduction in numbers of daily incontinence episodes at the end of treatment was only marginally improved in the Sativex group compared with placebo in the ITT population analysis, and did not reach statistical significance (Table 3).

There was a reduction in urinary urgency in favour of Sativex that approached statistical significance (Table 3). Similarly, the responder analysis (i.e. subjects with urgency at baseline but no episodes at the end of treatment) was in favour of Sativex but did not reach statistical significance.

When incontinence was ranked in order of severity in terms of the number of incontinence episodes per day, again there was a trend in favour of Sativex but no statistically significant difference.

The exploratory ANCOVA analysis of incontinence episode frequency in a subgroup of 49 subjects for whom post-void residual volumes were available showed a significant beneficial effect of Sativex in those with a residual volume <250 ml (−0.571 episodes per day, $p=0.0456$).

The number of daytime voids and the total number of voids per 24 h were significantly reduced in the Sativex group, as was the number of episodes of nocturia ($p=0.044$, $p=0.007$, $p=0.01$, respectively) (Table 3).

Table 2. Reasons for exclusion from efficacy analysis of per protocol data (some subjects had more than one reason for exclusion)

Reasons for non-inclusion for efficacy analysis	Sativex	Placebo
Total number of subjects	67	68
Violation of inclusion/exclusion criteria likely to affect efficacy	1	1
No record of study treatment record >50% days	5	3
Non-compliant with Visit 5 schedule	12	4
Use of prohibited drugs* (or change of dose) likely to effect primary endpoint during study period	4	7
Significant urinary tract infection	8	12
Change in diuretic during baseline	0	1
Baseline assessment >14 days prior to first dose of treatment	2	1
Total subjects excluded	21	23

*Prohibited drugs included tolterodine, oxybutinin, bendrofluazide, tamsulosin, methylprednisolone and prednisolone.

Sativex was significantly superior to placebo at all levels of severity of nocturia, but the size of effect was greater for more severely affected subjects (Figure 2); 16% of subjects on active treatment became nocturia free.

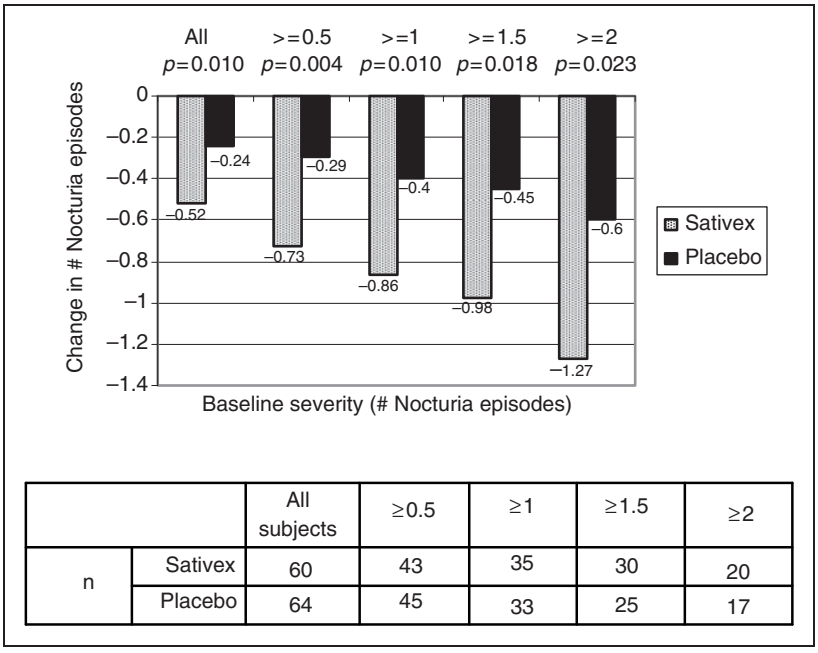
Daily use of incontinence pads and pad weight showed minimal treatment differences between Sativex and placebo (−0.08 pads per day and 11.4 g, respectively, in favour of Sativex) which were not statistically significant ($p = 0.74$ and $p = 0.76$, respectively).

The subject's opinion of OBC symptom severity (NRS) showed a significant difference in favour of Sativex at the end of treatment ($p = 0.001$) (Figure 3). Further analysis showed the difference between the two groups was increasingly marked as the symptom severity at baseline worsened. Subjects on the active treatment were three times more likely to report an improvement of more than 30% compared with those on placebo (odds ratio 3.07, CI 1.41, 6.97, $p = 0.006$). Figure 4 shows the PGIC scale data, which were highly significantly in favour of Sativex ($p = 0.005$). There was a trend in favour of improvement in I-QOL in the Sativex-treated group but this did not reach statistical significance (Table 3).

Table 3. Efficacy data – change from baseline to end of study

	Mean change from baseline				
	Sativex		Placebo		
Endpoint	*n*	Adjusted Mean	*n*	Adjusted Mean	*p*-value
Daily incontinence episodes	60	−1.08	64	−0.98	0.569
Total number of voids (per 24 h)	60	−1.75	64	−0.9	0.007
Number Daytime voids (per day)	60	−1.23	64	−0.66	0.044
Nocturia episodes (per day)	60	−0.52	64	−0.24	0.01
Void urgency episodes (per day)	60	−1.88	64	−1.12	0.07
Bladder symptom severity (Overall Bladder Condition) NRS	61	−2.21	66	−1.05	0.001
Incontinence QOL	59	14.3	61	10.4	0.166
Patient Global Impression of Change (recorded at end of study)	61	84% improve	67	58% improve	0.005

NRS, numerical rating scale; QOL, quality of life.



		All subjects	≥0.5	≥1	≥1.5	≥2
n	Sativex	60	43	35	30	20
	Placebo	64	45	33	25	17

Figure 2. Change in number of nocturia episodes related to severity of baseline episodes.

The mean voided volume per 24 h between the two groups was similar at baseline (active treatment group 1508 ml, placebo 1410 ml) and changed little by the end of the study (active treatment group 1425 ml and placebo 1385 ml). Urodynamic traces were evaluable for 10 subjects in each group; findings revealed a change in maximum cystometric capacity of +85 ml for the active treatment group and −10 ml for the placebo group. The difference was not significant between treatment groups.

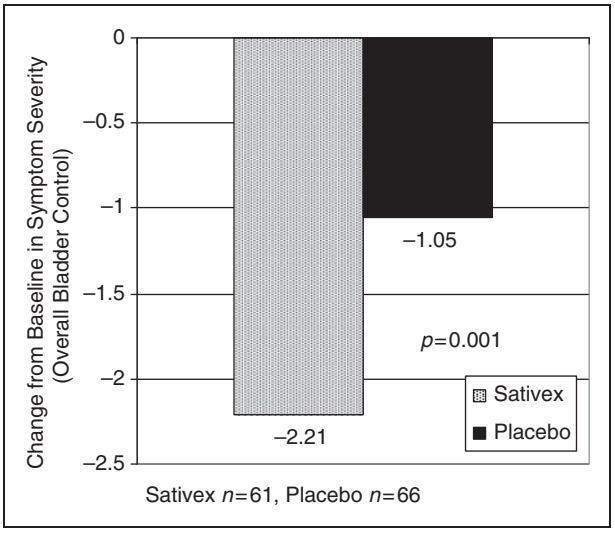


Figure 3. Subjects' opinion of bladder symptom severity (overall bladder condition). Subjects rated their condition on an 11-point scale (0 = no problems, 10 = intolerable problems).

Safety and tolerability results

Sativex was well tolerated in this study. There were no reported deaths during the study. Four subjects reported at least one serious adverse event (SAE) during the course of the study (two Sativex, two placebo). Three of the subjects reported SAEs that were considered treatment related; two were in the Sativex treatment group and one was in the placebo treatment group. One other placebo subject reported an MS relapse prior to treatment (placebo). A possible transient ischaemic attack (TIA) was reported for one Sativex subject 4 days after commencing study treatment, with symptoms of shaking, coordination problems and severe absence following a dose of 18 sprays in 1 day. Study treatment was withheld and the symptoms resolved. Sativex treatment was restarted the following day and the symptoms recurred a day later when the dose was again increased to 18 sprays. Based on the description of the event, there is a possibility that the episodes could have been caused due to intoxication rather than a TIA.

Haemorrhagic cystitis was reported in one Sativex subject approximately 1 month after commencing study treatment. The subject was treated with antibiotics, and developed a further SAE of dehydration, following a period of antibiotic-induced vomiting and diarrhoea. The haemorrhagic cystitis may have been related to the subject's underlying bladder instability.

One other placebo subject was hospitalized with dehydration and vomiting 8 days after completing

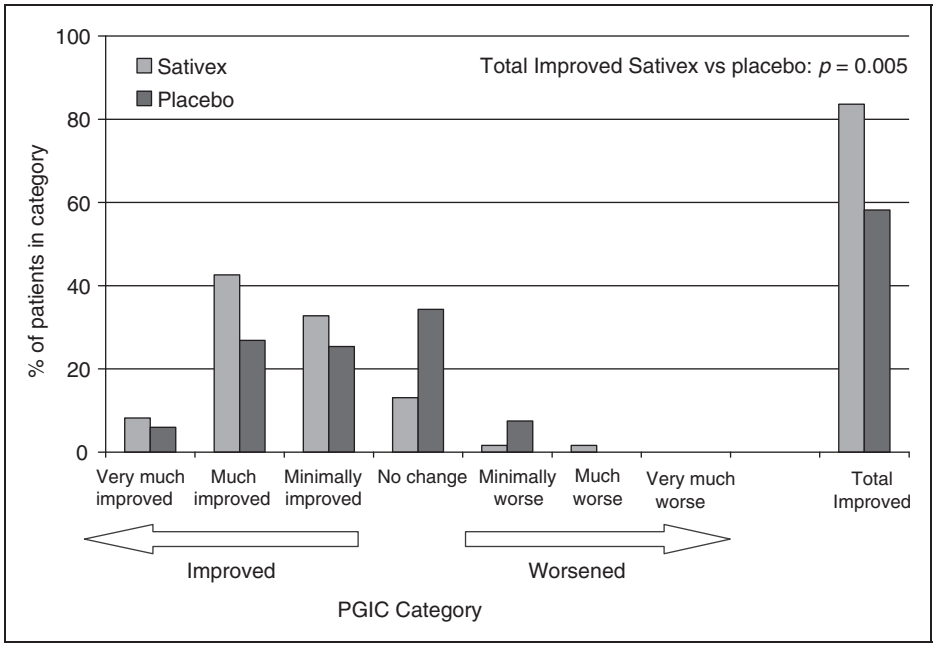


Figure 4. Histogram showing patients' global impression of change on Sativex or placebo.

60 days of study treatment. She was treated with trimethoprim, for an assumed urinary tract infection, and recovered.

Most AEs were considered mild or moderate in severity; many were possible CNS-type events (Table 4). Ten subjects stopped medication due to treatment-related AEs and withdrew from the study (seven on Sativex and three on placebo).

There were no significant changes in laboratory values or subjects' vital signs during the study. None of the subjects who were withdrawn from the study had clinically significant abnormal laboratory values.

At 50 min after the first dose of study medication, the mean intoxication score was 0.5 in the active treatment group and 0.4 in the placebo treatment group. At 2 h and 4 h after first dose, subjective mean intoxication scores were increased to 1.3 in the active treatment group and remained at 0.4 in the placebo treatment group. Mean scores at the final study visit were 1.4 for the active group and 0.2 in the placebo group. There was significant inter-individual variation in intoxication scores in both groups. The median scores were zero at all timepoints for both treatment groups.

Table 4. Adverse events on study medication. Events occurring in >5% of subjects.

	Number (%) of subjects			
	All causality		Treatment related	
All causality AEs Preferred Term	Sativex ($n=67$)	Placebo ($n=68$)	Sativex ($n=67$)	Placebo ($n=68$)
Dizziness#	12 (18%)	5 (7%)	12 (18%)	4 (6%)
Urinary tract infection	4 (6%)	7 (10%)	0	4 (6%)
Headache#	5 (8%)	5 (7%)	4 (6%)	2 (3%)
Vomiting	4 (6%)	2 (3%)	4 (6%)	2 (3%)
Nausea	3 (5%)	3 (4%)	3 (5%)	2 (3%)
Diarrhoea	2 (3%)	4 (6%)	2 (3%)	2 (3%)
Disorientation#	4 (6%)	1 (2%)	4 (6%)	1 (2%)
Weakness	3 (5%)	2 (3%)	3 (5%)	1 (2%)
Pharyngitis	3 (5%)	2 (3%)	2 (3%)	0
Nasopharyngitis	3 (5%)	1 (2%)	0	0
Dissociation#	4 (6%)	0	4 (6%)	0
Feeling drunk	3 (5%)	0	3 (5%)	0
Constipation	3 (5%)	0	2 (3%)	0
Balance impaired#	3 (5%)	0	3 (5%)	0
Paraesthesia#	3 (5%)	0	2 (3%)	0
Cystitis	3 (5%)	0	2 (3%)	0

# Denotes possible central nervous system-related AEs.

Discussion

The primary endpoint (i.e. reduction in number of episodes of incontinence per day) did not reach statistical significance in this randomized, double-blind, placebo-controlled trial in subjects with MS and severe bladder dysfunction. Despite this, Sativex did have some significant positive effects on other bladder symptoms.

There are a number of possible reasons why the primary endpoint failed to reach statistical significance in this study. One possible explanation may be the large placebo effect which was observed in this study. Such a large effect is characteristic of studies looking at bladder control,[20] and is thought to be due to observation and an effect of keeping a micturition diary. In addition, it should be noted that the subjects who were recruited in this study were subjects who had previously failed to respond adequately to existing medication and had residual bothersome bladder symptoms despite the best available treatment, and were receiving study medication as an add-on treatment (i.e. subjects were refractory to other treatments). As a result, not all subjects will respond to treatment (something which is frequently observed when assessing the efficacy of cannabinoids on other symptoms of MS, such as spasticity); this is unsurprising and it is unreasonable to expect all such subjects to respond to a new treatment.

Given that all subjects remained on existing treatment, this may have contributed to a relatively low baseline number of incontinence episodes per day (median baseline number of incontinence episodes per day was 1.23 for the active treatment and 1.32 for the placebo groups, respectively – this is lower than would normally be the case for clinical studies of subjects with OAB who have been through a washout period). The inclusion criterion of a minimum of three incontinence episodes in 5 days meant that subjects with an average of 0.6 episodes a day were eligible for study entry, leaving little room for sufficient improvement to detect a significant difference between treatments. In addition, it is also possible that this treatment may have a limited effect on incontinence and more favourable effects on other bladder endpoints, such as frequency, urgency or nocturia.

The other issue worthy of note in this study is the difference in the size of the ITT population ($n=135$ subjects) and the PP population ($n=86$ subjects). This high proportion of exclusions ($n=46$) illustrates the difficulty in maintaining subject compliance with the study protocol; however, these exclusions were equally distributed between active and placebo groups ($n=23$ per group). Many of the protocol deviations were due to non-compliance in terms of the final visit assessment date and actual date of last dose of treatment (i.e. the

end of treatment assessments were not done whilst subjects were still on treatment or within 24 h of their last dose of 8 weeks of study treatment; 16 subjects). The fact that 20 subjects had a urinary tract infection (either at baseline or during treatment) further confounded the assessment of the study endpoints. Some subjects had more than one deviation, which excluded them from the PP population.

Freeman et al. reported on the effect of cannabis on urge incontinence in subjects with MS, comparing the oral administration of cannabis extract, THC and a matching placebo (the CAMS-LUTS study).[21] It was found that there was a significant difference in the number of episodes of incontinence between the cannabinoid treatment groups and the placebo group. This study used a different protocol, different active treatment and a larger number of subjects. An earlier open-label pilot study by Brady et al. demonstrated a reduced incidence of incontinence episodes following treatment with Sativex or THC extract.[2]

Sativex had a significant beneficial effect on other key parameters associated with OAB: urgency, nocturia and urinary frequency, and on the subject's assessment of the severity of their symptoms. As the urine volumes in the two groups (active and placebo) pre- and post-treatment were almost equal, these effects cannot be attributed to a change in urine volume, which was used as a surrogate marker for fluid intake.

There was also a significant improvement in subject perception of bladder symptom severity score which was mirrored in the PGIC results. Overall, despite the failure to hit the primary endpoint of the study, and the fact that there was no allowance made for multiplicity, taking into account the proportion of secondary outcomes that were positive and the levels of significance observed, this study does provide clinical evidence across a range of bladder-related endpoints that Sativex has some beneficial effect when used for treatment of the bladder symptoms in patients with MS. Similar symptomatic improvement has been reported in subjects with spasticity and pain.[22–24]

Another notable finding from the review of the concomitant medications taken by study subjects was that subjects in the placebo group appeared to use more prohibited drugs during the study than those in the Sativex group. This suggests improved efficacy within the Sativex group resulted in subjects requiring less in the way of additional medications to control their symptoms. Similarly, subjects in the placebo group took approximately twice as many sprays per day of study medication compared with those in the Sativex group, which could be considered as evidence that Sativex subjects achieved benefit (symptom control) from treatment at a lower dose of self-administered medication than those on placebo.

Blinding of treatment to subjects did not appear to be an issue in this study. The rates of self-reported mean 'intoxication' scores using an 'Intoxication' 0–10 NRS (using the anchors 0 = No intoxication and 10 = Extreme intoxication) were very similar between active and placebo groups, the greatest difference being observed at 2 h post-dose on Day 1 (change from baseline in mean NRS score = 1.2 (out of 10) on active compared with 0.4 on placebo). As with previous studies of Sativex in patients with MS, the data provide no evidence that the change from baseline in bladder symptoms was affected by prior use of cannabis overall or in combination with treatment group, or by CNS AE profile. The dosing of study drug (mean number of sprays per day) did not differ between the prior cannabis users and the cannabis-naïve subjects, neither overall, nor within each treatment group. This suggests that even if prior users of cannabis were able to distinguish between the treatments, this did not lead to bias in the assessment of efficacy. The most common CNS disorder reported as an AE in this study was dizziness (17.9% Sativex, 7.4% placebo) – all other CNS-type AEs in this system organ class were below 5% in incidence in the Sativex group. This was a relatively low incidence of dizziness compared with other studies of Sativex in patients with MS. The only other AEs over 5% incidence on Sativex were disorientation (6% Sativex vs. 1.5% placebo) and dissociation (6% Sativex vs. 0% placebo).

There are a number of limitations to this study. As discussed above, a number of factors may have contributed to a relatively low severity of incontinence at baseline, thereby contributing to the lack of significance with regard to the primary endpoint. In addition, in the analyses undertaken on these study data no allowance for multiplicity was made. However, it should be noted that there is a valid reason for this, in that a number of the variables measured in this study are not independent variables and indeed some are the direct sums of others – hence the use of a classical Bonferroni correction is inappropriate on this occasion. Thus, despite the lack of correction for multiplicity, it can be observed that the study endpoints (although multiple) are measuring similar variables in different ways and, within this framework, some consistency between endpoints has been obtained in this study. Thus, from this perspective, there is some consistent evidence that Sativex provided benefit with regard to certain bladder symptoms to the subjects in this study. One should bear both of these factors in mind when considering the data.

Also, the study had a number of subjects which were not available for the PP analysis. While the reasons for the exclusion were justified, this is not helpful when drawing conclusions from the study. Further, only small numbers of subjects had evaluable

cystometric traces. Similar findings for urodynamic investigations were reported in the CAMS subset study.[21]

Sativex appears to be well tolerated in patients suffering from MS – there were no deaths in the study, and only two SAEs were reported on treatment. The majority of AEs reported in this study (>80%) were mild to moderate in nature. Only 10 subjects withdrew from treatment due to AEs ($n=7$ Sativex, $n=3$ placebo), reflecting the tolerability. The mean doses of 9 sprays per day Sativex administered are comparable to those in previous studies in MS subjects.[22–24,27–29] There was no assessment of the double-blind study design effectiveness or potential unblinding within the study population group. An independent reviewer has previously assessed the possibility of unblinding against AE profiles in studies using comparable doses of Sativex.[30] There is no evidence to suggest that participants who have or have not previously used cannabis would be able to identify Sativex treatment from experiencing an AE from the Sativex profile. No safety concerns were identified and most of the reported AEs have been observed in other clinical trials of Sativex.[22–24,25–27] However, further long-term[28,29] data need to be evaluated.

Further studies investigating the mechanism of action of cannabinoids on bladder function may reveal more information about cannabinoid receptor expression and provide evidence as to the role of cannabinoid modulators in bladder control. Work by one of the co-authors (DD) suggests that CB_1 and CB_2 receptors are present on the human bladder, and that the beneficial effect of cannabinoid agonists in bladder function may not only be due to a cannabinoid action in the brain but also due to a peripheral contribution, either to activation of cannabinoid receptors at the spinal level or of those located in the bladder, or both.[31–33] In addition, it is known that the endocannabinoid anandamide has activity at the $TRPV_1$ receptor, which is also thought to regulate the frequency of bladder reflex contractions[34] Further, it has been reported that CB2 receptor expression is increased in acutely and chronically inflamed bladder of rats.[35] Given that it has been reported that endocannabinoids and cannabinoid agonists decrease motility in normal and inflamed bladder,[35] it is possible that the endocannabinoid system or related systems (such as the vanilloid system) may mediate functional effects of such compounds on the bladder.

As the neurological condition of patients with MS deteriorates, management of bladder symptoms can be difficult. Many anticholinergic drugs are less than ideal due to lack of efficacy, or because they are not well tolerated due to side effects. Recently intradetrusor injections of botulinum toxin have come to the fore in managing these patients' bladder symptoms, but intermittent self-catheterization is almost always necessary following injections.[36] There is therefore a need for a less invasive treatment, and the additional beneficial effects of Sativex on spasticity, spasms, pain and sleep mean that this therapy should be included in the armamentarium used to treat the troublesome bladder symptoms of MS.

Acknowledgements

The authors would like to thank all the other Investigators involved in this study: Dr W Notcutt, (Great Yarmouth, UK), Dr M Sharief, (London, UK), Professor CD Ward, Derby (UK), Dr J O'Riordan (Dundee, Scotland, UK), Dr L Vande Gaer (Lommel, Belgium), Mr RJ Webb (Norwich, UK), Mr WH Turner (Cambridge, UK), Dr S Ahmed (London, UK), Mr AJ Arnold (Birmingham, UK), Dr Minea (Brasov, Romania), Dr C Zaharia (Craiova, Romania), Dr E Tufanoiu (Bucuresti, Romania), Dr M Pereanu (Sibiu, Romania) Dr M Protosevici (Bucuresti, Romania), Mr I Eardley (Leeds, UK). We would also like to thank the patients who participated in this study and their families. We also thank all the study site staff who assisted with the study: We acknowledge Miss Gonzales' important contributions to patient management. We acknowledge the role of GW Pharma Ltd. as sponsor of the study.

Funding

This trial was sponsored and fully funded by GW Pharma Ltd. Investigators received research grants from GW Pharma Ltd to cover the costs of the study.

Conflict of interests

RK and CC have received sponsorship from GW Pharma Ltd to attend relevant conferences/scientific meetings and are paid consultants for GW Pharma Ltd. CS is an employee of GW Pharma Ltd.

References

1. Abrams P, Cardoza L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. *Neurourol Urodyn* 2002; 21: 167–178.
2. Brady CM, DasGupta R, Dalton C, Wiseman OJ, Berkley KJ and Fowler CJ. An open-label pilot study of cannabis-based extracts for bladder dysfunction in advanced multiple sclerosis. *Mult Scler* 2004; 10: 425–433.
3. Milsom I, Abrams P, Cardoza L, Roberts RG, Thuroff J and Wein AJ. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. *BJU Int* 2001; 87: 760–766.
4. Russo E. Cannabis treatments in obstetrics and gynaecology: A historical review. *J Cannabis Therapeut* 2002; 2: 5–35.
5. Russo EB. The role of cannabis and cannabinoids in pain management. In: Cole BE, Boswell M (eds) *Weiner's Pain Management: A Practical Guide for Clinicians*, 7th ed. Boca Raton, FL: CRC Press, 2006, pp.823–844.

6. British Medical Association. *Therapeutic Uses of Cannabis*. Amsterdam: Harwood Academic Publishers, 1997, pp.1–6.
7. Royal College of Physicians. *Cannabis and Cannabis based medicines: potential benefits and risks to health. Report of a working party*. London: RCP, 2005.
8. Dmitrieva N and Berkley KJ. Contrasting effects of WIN 55212-2 on motility of the rat bladder and uterus. *J Neurosci* 2002; 22: 7147–7153.
9. Jaggar SI, Hasnie FS, Sellaturay S and Rice AS. The anti-hyperalgesic actions of the cannabinoid anandamide and the putative CB2 receptor agonist palmitoylethanolamide in visceral and somatic inflammatory pain. *Pain* 1998; 76: 189–199.
10. Farquhar-Smith WP and Rice AS. Administration of endocannabinoids prevents a referred hyperalgesia associated with inflammation of the urinary bladder. *Anesthesiology* 2001; 94: 507–513.
11. Bartocci C, Evandri MG, Tucci P and Bolle P. Interactions between delta-9THC and capsaicin on isolated lamb bladder detrusor. *Farmaco* 2001; 56: 349–351.
12. Costa B, Giagnoni G, Franke C, Trovato AE and Calleoni M. Vanilloid TRPV1 receptor mediates the anti-hyperalgesic effect of the non-psychoactive cannabinoid, cannabidiol, in a rat model of acute inflammation. *Br J Pharmacol* 2004; 143: 247–250.
13. Apostolidis A, Yiangou Y, Brady CM, Ford AP, Baecker PA, Jacques TS, et al. Increased urothelial expression of capsaicin receptor TRPV1 in human urinary bladder disorders and decrease after intravesical resiniferatoxin (RTX) treatment. *Br J Urol Int* 2004; 93: 336–340.
14. Hohmann AG and Herkenham M. Regulation of cannabinoid and mu opioid receptors in rat lumbar spinal cord following neonatal capsaicin treatment. *Neurosci Lett* 1998; 252: 13–16.
15. Nicholson AN, Turner C, Stone BM and Robson P. Effect of [DELTA]-9-tetrahydrocannabinol and cannabidiol on nocturnal sleep and early-morning behavior in young adults. *J Clin Psychopharmacol* 2004; 24: 305–313.
16. Lastres-Becker I, Molina-Holgado F, Ramos JA, Mechoulam R, Fernandez-Ruiz J. Cannabinoids provide neuroprotection against 6-hydroxydopamine toxicity in vivo and in vitro: relevance to Parkinson's disease. *Neurobiology of Disease* 2005; 19(1–2): 96–107.
17. Iuvone T, Esposito G, Esposito R, Santamaria R, Di Rossa M and Izzo AA. Neuroprotective effect of cannabidiol, a non-psychoactive component from Cannabis sativa, on beta-amyloid-induced toxicity in PC12 cells. *J Neurochem* 2004; 89: 134–141.
18. Consroe P, Musty R, Rein J, Tillery W and Pertwee R. The perceived effects of smoked cannabis on patients with multiple sclerosis. *Eur Neurol* 1997; 38: 44–48.
19. Wagner TH, Patrick DL, Bavendam TG, Martin ML and Buesching DP. Quality of life of persons with urinary incontinence: development of a new measure. *Urology* 1996; 47: 67–72.
20. van Leeuwen JH, Castro R, Busse M and Bemelmans BL. The placebo effect in the pharmacologic treatment of patients with lower urinary tract symptoms. *Eur Urol* 2006; 50: 440–453.
21. Freeman RM, Adekanmi O, Waterfield MR, Waterfield AE, Wright D and Zajicek J. The effect of cannabis on urge incontinence in patients with multiple sclerosis: a multicentre, randomised placebo-controlled trial. *Int Urogynecol J Pelvic Floor Dysfunct* 2006; 17: 636–641.
22. Rog DJ, Nurmikko TJ, Friede T and Young CA. Randomised, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. *Neurology* 2005; 65: 812–819.
23. Wade DT, Makela P, Robson P, House H and Bateman C. Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomised, placebo-controlled study on 160 patients. *Mult Scler* 2004; 10: 434–441.
24. Collin C, Davies P, Mutiboko IK and Ratcliffe S. Randomized controlled trial of cannabis-based medicine in spasticity caused by multiple sclerosis. *Eur J Neurol* 2007; 14: 290–296.
25. Barnes MP. Sativex: clinical efficacy and tolerability in the treatment of symptoms of multiple sclerosis and neuropathic pain. *Expert Opin Pharmacother* 2006; 7: 607–615.
26. Perras C. Sativex for the management of multiple sclerosis symptoms. *Issues Emerg Health Technol* 2005; 72: 1–4.
27. Nurmikko TJ, Serpell MG and Hoggart B. Sativex successfully treats neuropathic pain characterised by allodynia: A randomised, double-blind, placebo-controlled clinical trial. *Pain* 2007; 133: 210–220.
28. Rog DJ, Nurmikko TJ and Young CA. Oromucosal delta-9–tetrahydrocannabinol/cannabidiol for neuropathic pain associated with Multiple Sclerosis: An uncontrolled, open-label, 2-year extension trial. *Clin Ther* 2007; 20: 2068–2079.
29. Wade DT, Makela PM, House H, Bateman C and Robson P. Long-term use of a cannabis-based medicine in the treatment of spasticity and other symptoms in multiple sclerosis. *Mult Scler* 2006; 12: 639–645.
30. Altman D. Assessment of blinding in phase III Sativex spasticity studies. Data on File. (GW Pharma Ltd, 28 July 2006).
31. Blyweert W, Van Der Aa F and De Ridder D. Cannabinoid therapy in detrusor overactivity: local versus systemic effect in a spinalised rat model. *Neurol Urodyn* 2003; 22: 379–380.
32. Ost T, Roskams D and De Ridder D. Immunohistochemical study of the cannabinoid receptors CB1 and CB2 in the human bladder. *Mult Scler* 2001; S24.
33. Ost F, Van Der Aa F and De Ridder D. Intravesical application of the endogenous cannabinoid anandamide in the rat model: preliminary data. *Mult Scler* 2001; 7: S17.
34. Avelino A and Cruz F. TRPV1 (vanilloid receptor) in the urinary tract: expression, function and clinical applications. *Naunyn Schmiedebergs Arch Pharmacol* 2006; 373: 287–299.
35. Merriam FV, Wang ZY, Guerios SD and Bjorling DE. Cannabinoid receptor 2 is increased in acutely and chronically inflamed bladder of rats. *Neurosci Lett* 2008; 445: 130–134.
36. Kalsi V, Fowler C and Dasgupta P. The use of botulinum toxin injections to treat the overactive bladder. *ACNR* 2005; 5: 34–35.