Editor's Choice

Efficacy and safety of nabiximols cannabinoid medicine for paediatric spasticity in cerebral palsy or traumatic brain injury: a randomized controlled trial

CHARLIE FAIRHURST[1] | RAM KUMAR[2] | DANIEL CHECKETTS[3] | BOLA TAYO[3] | SUSIE TURNER[1]

1 Department of Paediatric Neurosciences, Evelina London Children's Hospital, Guy's and St Thomas' NHS Foundation Trust, London, **2** Department of Paediatric Neurology, Alder Hey Children's Hospital, Liverpool, **3** GW Research Ltd, Cambridge, UK.

Correspondence to Charlie Fairhurst at Department of Paediatric Neurosciences, Evelina London Children's Hospital, Guy's and St Thomas' NHS Foundation Trust, Westminster Bridge Road, London, SE1 7EH, UK. E-mail: charlie.fairhurst@gstt.nhs.uk

This article is commented on by Hall and Nielsen on page 1007 of this issue.

PUBLICATION DATA
Accepted for publication 2nd March 2020.
Published online 27th April 2020.

ABBREVIATIONS

CBD	Cannabidiol
MAS	Modified Ashworth Scale
MTS	Modified Tardieu Scale
NRS	Numerical Rating Scale
OLE	Open-label extension
SAE	Serious adverse events
THC	Tetrahydrocannabinol

AIM To assess the efficacy, safety, and tolerability of oromucosal nabiximols cannabinoid medicine as adjunct therapy for children with spasticity due to cerebral palsy/traumatic central nervous system injury with inadequate response to existing treatment.
METHOD Overall, 72 patients (mean [SD] age 12y 4mo [3y 1mo], range 8–18y) were randomized at a ratio of 2:1 to receive nabiximols (*n*=47; 29 males, 18 females) or placebo (*n*=25; 15 males, 10 females) for 12 weeks (12 sprays/day max. based on clinical response/tolerability). The primary outcome was change from baseline in level of spasticity on a 0 to 10 Numerical Rating Scale (NRS), assessed by the primary caregiver at 12 weeks. Secondary outcomes included additional measures for spasticity, sleep quality, pain, health-related quality of life, comfort, depression, and safety.
RESULTS There was no significant difference in the spasticity 0 to 10 NRS between nabiximols versus placebo groups after 12 weeks. No statistically significant differences were observed for any secondary endpoint. Adverse events were predominantly mild or moderate in severity; however, three cases of hallucinations were reported.
INTERPRETATION Nabiximols was generally well tolerated; however, neuropsychiatric adverse events were observed. No significant reduction in spasticity with nabiximols treatment versus placebo was observed.

Cannabinoids have been used medicinally for thousands of years.[1] The ability of plant-based cannabinoids to manage spasms was discovered by a variety of cultures around the world to treat conditions such as tetanus.[2] Two main endocannabinoid receptors have been identified in the central nervous system (CNS): presynaptic CB_1 receptors in the basal ganglia nuclei, hippocampus, cortex, and cerebellum; and CB_2 receptors predominantly in the periphery.[3]

The principal constituents of Cannabis sativa are tetrahydrocannabinol (THC) and cannabidiol (CBD), both of which possess the potential to modify muscle tone.[4] The primary pharmacological effects of THC include analgesia, muscle relaxation, antiemesis, appetite stimulation, and psychoactive properties.[1] Those of CBD include anticonvulsant, muscle relaxant, anxiolytic, antioxidant, and antipsychotic activity.[1]

Widespread societal and clinical interest in medicinal cannabis use to reduce pain and spasticity in patients with demyelinating diseases, such as multiple sclerosis, has intensified over the last two decades.[5] To date, most clinical trials examining the efficacy of treating spasticity with cannabinoids have been conducted in adults.[6]

Several randomized controlled trials[7–14] and an open-label extension (OLE) study[15] were undertaken in adult patients with multiple sclerosis using either oral cannabis extracts or Sativex® (THC:CBD [nabiximols oromucosal spray]). Nabiximols is a whole plant extract from Cannabis sativa L, purified to contain defined and consistent amounts of CBD, THC, and additional cannabinoid and non-cannabinoid components, and is a highly regulated prescription drug rather than a herbal preparation.[16] Previously, the ability of these treatments to alleviate neuropathic pain and spasticity was investigated in adult patients. Primary outcomes looked at levels of spasticity and central pain using a spasticity 0 to 10 Numerical Rating Scale (NRS) and pain 0 to 10 NRS, implemented as self-reported measures. The trials conducted with nabiximols led to a marketing authorization of Sativex for the treatment of spasticity in adults with multiple sclerosis who did not derive enough benefit from conventional antispasticity medications across a number of major markets.[6]

This multicentre, randomized, placebo-controlled trial was designed to investigate the efficacy and safety of nabiximols versus placebo on spasticity in paediatric patients (8–

18y). Children with a non-progressive upper motor neurone syndrome associated with cerebral palsy or another CNS injury after birth were included as they were considered to have a high degree of spasticity or increased muscle tone leading to potential functional impairment and discomfort. Because of the challenges of assessing and measuring spasticity in a paediatric population, a mixture of subjective (self-reported and caregiver-reported) and objective (observer-rated) primary and secondary endpoint measures were used to assess muscle tone, motor function, daily functioning, comfort, sleep quality, mood, and quality of life.

METHOD

Trial design

All relevant trial-related documents, including the protocol, were reviewed by the independent ethics committees or institutional review boards governing each investigational site. The trial was performed between 27th December 2013 and 23rd March 2017 at 11 sites in the UK, two in Israel, and one in the Czech Republic. The Clinicaltrials.gov registration number is NCT01898520. The trial was given full ethical approval by the Leeds West National Research Ethics Service committee (MREC reference 13/YH/0201) and all sites in the UK undertook Site Specific Information submissions to the National Institute for Health Research. Further details of the centres involved are included in the Acknowledgements. As it was expected most patients would have an insufficient level of understanding of what was proposed, parental or legal representative consent was sought for participation in the trial and for results to be published. In cases where the patient did possess adequate understanding, assent was taken in conjunction with parental or legal representative consent. The trial was performed in full conformity with the current Declaration of Helsinki,[17] International Council on Harmonization guidelines for good clinical practice,[18] and all other applicable regulations.

During the trial there were two amendments to the protocol. In both cases, minor updates were made, each to clarify one of the inclusion criteria, and included administrative changes to aid clarity. The objectives of this prospective, randomized, multicentre, placebo-controlled trial were to investigate the efficacy, safety, and tolerability of nabiximols versus placebo in paediatric patients with non-progressive spasticity. The trial was conducted in two phases. The first was a double-blind, randomized, placebo-controlled phase followed by an OLE phase.

After a 1-week baseline observation phase, patients gave informed consent then were randomized (double-blind) in a 2:1 ratio to receive either nabiximols or placebo. Each 100μL actuation of nabiximols delivers 2.7mg THC, 2.5mg CBD, and additional cannabinoid and non-cannabinoid components to the sublingual or oral mucosa. Patients titrated nabiximols or placebo over a period of 9 weeks to a maximum of 12 sprays per day, or until they experienced intolerable side effects. Patients could stop titrating at any point dependent on tolerance (i.e. presence of unacceptable side effects) or perceived maximal effect. Patients continued to administer their assigned treatment at their individually determined dose for a further 3 weeks (12wks treatment in total). During treatment, visits to the clinic occurred every 4 weeks, with telephone consultations between each visit. Treatment was otherwise administered at home. Patients were then invited to continue in a 24-week OLE phase, during which there was a retitration of nabiximols over 9 weeks. If patients did not wish to continue, a safety follow-up call was made 14 days after the end of treatment.

Exposure to the oromucosal spray was recorded in the daily diary as the number of sprays used.

What this paper adds

- Oromucosal nabiximols is generally well tolerated by paediatric patients.
- However, three cases of hallucinations were observed, one of which involved auditory hallucinations and a suicide attempt.
- Oromucosal nabiximols versus placebo did not reduce cerebral palsy/central nervous system injury-related spasticity.

Randomization to treatment

At screening, all patients were allocated a unique patient code assigned by the site and the last three digits ascended in numerical order at each site. After screening and the baseline period, participants who satisfied the entry criteria were randomized. An independent statistician produced a treatment allocation schedule using balanced randomly permuted blocks using a computer-based algorithm. Randomization numbers were listed as unique numbers. The randomization was balanced within trial sites. The randomization schedule was held by the clinical trials supplies department of the sponsor and not divulged to any other person involved in the trial until the database was locked.

Blinding

During the trial, the treatment assignment code list was available only to the trial statistician and the clinical trials supplies operations group. Except in cases of emergency unblinding, patients, investigational site personnel, sponsor employees, and all other trial personnel remained blinded to the identity of the treatment assignments until every patient had completed trial treatment and the database had been locked.

Sample size

Sample size calculations were based on the primary endpoint of change in spasticity on a 0 to 10 NRS score from baseline. Patients were to be expected, on average, to have a score of around 5 at baseline. In order to achieve 80% power to detect a mean difference between treatments of 1.5 NRS points, with a common standard deviation (SD) of 2.1 and using a two-tailed test at a 5% significance level, and with a 2:1 randomization, the trial required 48 patients in the nabiximols group and 24 in the placebo group

(when the 72 were randomized it could not be certain that the ratio would be perfect 2:1).

Trial population

Inclusion criteria included, among others: (1) children aged 8 to 18 years with spasticity due to cerebral palsy or traumatic, non-progressive CNS injury; (2) Gross Motor Functional Classification System level III to V; (3) under treatment for at least 1 year with at least one named agent for treatment of motor disorder (baclofen, diazepam [or other benzodiazepine], dantrolene, tizanidine, gabapentin, or trihexyphenidyl) with inadequate efficacy or unacceptable side effects; (4) background neurological drug regimen should not be altered during the trial period; (5) during the baseline observation phase, a Modified Ashworth Scale (MAS) score of 2 or more as assessed by a trained health care professional in at least one muscle group and a minimum average spasticity 0 to 10 NRS score of more than 4 as assessed by the primary caregiver (sum of last 6d before randomization >24).

Exclusion criteria included, among others: (1) treatment with botulinum neurotoxin A in the previous 12 weeks or expected need for concomitant use during randomized phase; (2) any history of schizophrenia or other psychotic illness in the patients themselves or a first-degree relative; (3) planned surgery during study; (4) weight less than 15kg.

Trial assessments

To ensure consistency with the randomized controlled trials of nabiximols in adult patients with spasticity due to multiple sclerosis, the recommendation from the Paediatric Committee of the European Medicines Agency was that the primary endpoint for efficacy should be a spasticity 0 to 10 NRS, in this case reported by the primary caregiver as the patient's proxy. The caregiver was asked how their child's muscles had felt on that day, 0 being 'my child's muscles have felt totally relaxed' and 10 being 'my child's muscles have felt the tightest/hardest they have ever felt'.

The primary caregiver reported the spasticity 0 to 10 NRS score in a diary at the same time each day during the randomized phase and weekly during the OLE phase. The endpoint for analysis was the comparison between nabiximols versus placebo for change in daily spasticity 0 to 10 NRS score from baseline (mean of final 7d of baseline period) to the end of the randomized phase (mean of final 7d before completion/withdrawal).

Several secondary endpoints were also used to evaluate efficacy in terms of clinical observation of muscle tone, motor function, daily functioning, comfort, sleep quality, mood, and quality of life, using validated assessment tools. These were: (1) spasticity measures: the MAS and Modified Tardieu Scale (MTS), both measured in standardized and reproducible form by trained paediatric physiotherapists at each clinic visit during the trial. Site training was performed to minimize the risk of interobserver bias. Where possible, the same examiner was used each time to reduce intraobserver variability. The MAS evaluation was performed on three upper and three lower limb muscle groups while the MTS was performed on the worst affected limb only. (2) Sleep quality, assessed by validated 0 to 10 NRS (1 being 'my child had a night of non-stop sleep' and 10 being 'my child was unable to sleep at all'). (3) Background pain associated with musculoskeletal factors and comorbidity was considered at baseline and at each clinic visit using the Paediatric Pain Profile, a 20-item behaviour rating scale completed by the caregiver.[19] Each item was scored on a 4-point scale of 0 to 3 as having occurred 'not at all' to 'a great deal' in the given time period. The total score ranged from 0 to 60. (4) Comfort was also subjectively recorded daily in the diary as the length of time in minutes that the individual child or adolescent could maintain a sitting or lying posture without obvious discomfort. (5) Both patient and caregiver quality of life measures were recorded at each clinic visit using validated age appropriate scales: the Cerebral Palsy Quality of Life – Child/Teen Questionnaire[20] and caregiver quality of life questionnaire (Short Form 36-item Health Survey).[21] The primary caregiver completed both questionnaires. For the Cerebral Palsy Quality of Life – Child/Teen Questionnaire, caregivers were asked to assess how they thought the patient felt about the aspects of their life covered. (6) A Children's Depression Inventory 2[22] was completed by all children who were able to respond to questions at each clinic visit, to monitor for the emergence of any depressive symptoms. (7) A 7-point scale of caregiver's global impression of change in the patient's general functional abilities and ease of transfer was completed at each clinic visit.

Safety was monitored by adverse event reporting throughout the trial and by direct questioning at every telephone contact or clinic visit. Full physical and oral examinations were undertaken, including clinical laboratory serology and urine testing and a 12-lead electrocardiogram at screening, the end of randomized phase, and the end of the OLE phase. Vital signs were recorded in a sitting position at every clinic visit. Height and weight and postural changes in blood pressure and pulse rate were recorded at the beginning and end of each study phase.

Statistical analysis

Endpoint analysis of the randomized phase considered baseline as the average daily 0 to 10 NRS score of Day –7 to Day –1, and endpoint as the average of the last 7 days up to the earliest date of any of the following: Day 84, last diary entry, or last dose of nabiximols or placebo.

Primary analysis was a comparison of change from baseline between treatment groups using analysis of covariance (ANCOVA) with baseline score as a covariate and treatment as a fixed effect. A two-sided significance test was used in all comparisons at the 5% level of significance. Sensitivity analysis of the primary endpoint was undertaken using mixed model repeated measures on the observed data through the trial.

For each continuous secondary efficacy endpoint (sleep 0 to 10 NRS, MTS, MAS, Cerebral Palsy Quality of Life – Child/Teen Questionnaire, Children's Depression Inventory 2, Paediatric Pain Profile, caregiver quality of life questionnaire Short Form 36-item Health Survey, and comfort questionnaire), an ANCOVA model was fitted for the change from baseline score at the end of treatment, with the baseline value of the corresponding measurement as a covariate and treatment as a fixed effect. For the categorical secondary efficacy endpoint, caregiver's global impression of change, an ordinal logistic regression model was used to assess the caregiver's global impression of change response at the end of treatment, with caregiver's global impression of change response as the dependent variable and treatment as a factor.

There were three analysis sets for this study, as follows. (1) Intention to treat analysis set: the primary analysis set for all efficacy endpoints, which included all patients who received nabiximols or placebo. (2) Per protocol analysis set: all patients who completed the trial with no protocol violations deemed to compromise the assessment of the efficacy. (3) Safety analysis set: all patients who received at least one dose of nabiximols or placebo.

In all analysis sets, patients were analysed (using SAS version 9.3 or higher; SAS Institute, Cary, NC, USA) according to the treatment group they were randomized.

RESULTS

In total, 85 patients were screened; 13 were screen failures leading to 72 patients enrolled into the randomized phase (61 in the UK, seven in Israel, and four in the Czech Republic). Treatment was provided in a double-blind manner with patients randomized 2:1 to receive nabiximols (n=47) or placebo (n=25).

A total of four (6%) patients withdrew during the randomized phase, three in the nabiximols group and one in the placebo group. Two (3%) patients (both taking nabiximols) withdrew because of treatment-emergent adverse events (see 'Safety' section below). The third patient taking nabiximols was withdrawn by the investigator 31 days into the treatment period because of non-compliance, comorbid scoliosis, and orthopaedic surgery brought forward. One patient taking placebo withdrew consent 6 weeks into the treatment period because of difficulty administering the spray. In total, 44 patients taking nabiximols completed the trial and 24 patients taking placebo completed the trial.

All randomized patients were included in the intention to treat analysis set. The per protocol analysis set included 42 patients in the nabiximols group and 21 patients in the placebo group. Nine (13%) patients in total were excluded from the per protocol analysis set for the following reasons: change in background antispasticity medication in trial (one in the nabiximols group and two in the placebo group); insufficient time on established dose (three in the nabiximols group and two in the placebo group); or planned orthopaedic surgery during treatment phase (one in the nabiximols group).

In total, 67 out of 68 (99%) patients who completed the randomized phase entered the OLE phase, of whom 54 (81%) completed the OLE phase. In the OLE phase, 6 out of 43 patients assigned to nabiximols during the randomized phase (active-to-active) subsequently withdrew; three because of adverse events, two because of withdrawal of consent, and one because of withdrawal by an investigator for non-compliance to the study protocol. In the OLE phase, 7 out of 24 patients assigned to placebo during the randomized phase (placebo-to-active) subsequently withdrew; six because of adverse events and one because of withdrawal of consent.

Demographics

The demographics of the patients who took part in the trial are outlined in Table 1. There were no significant differences in baseline characteristics between the nabiximols and placebo arms of the randomized group. Most patients (89%) enrolled across the two treatment groups had cerebral palsy as the underlying cause of spasticity.

Exposure

In the randomized phase, there was no significant difference in the number of the oromucosal sprays used in the nabiximols and placebo arms. The mean number of daily sprays administered by those taking nabiximols was 5.82 (SD 1.62), with a maximum of 7.69 over the randomized phase duration. In the placebo group, the mean number of daily sprays administered was 6.04 (SD 1.88), with a maximum of 8.07 over the duration of the randomized phase. One individual withdrew from the active group because of an adverse event of retching, and 10 others reported retching and/or vomiting. Four patients taking placebo also

Table 1: Patient demographics and baseline characteristics; randomized phase (safety set)

Characteristic	Nabiximols (n=47)	Placebo (n=25)
Sex, *n* (%)		
Male	29 (61.7)	15 (60.0)
Female	18 (38.3)	10 (40.0)
Ethnicity, *n* (%)		
White	42 (89.4)	21 (84.0)
Black	1 (2.1)	1 (4.0)
Asian	1 (2.1)	2 (8.0)
Other	3 (6.4)	1 (4.0)
Age (y:mo)	12:7 (3:4)	11:11 (2:5)
Height (m)	1.34 (0.185)	1.34 (0.160)
Weight (kg)	34.0 (14.6)	31.3 (10.2)
BMI (kg/m^2)	18.2 (4.78)	17.1 (3.55)
Cerebral palsy, *n* (%)	43 (91.5)	21 (84.0)
Traumatic CNS injury, *n* (%)	4 (8.5)	4 (16.0)
Time since diagnosis (y:mo)	10:4 (4:3)	10:6 (3:7)
GMFCS level, *n* (%)		
III	1 (2.1)	0
IV	10 (21.3)	10 (40.0)
V	36 (76.6)	15 (60.0)

Data are mean (SD) unless otherwise stated. SD, standard deviation; BMI, body mass index; CNS, central nervous system; GMFCS, Gross Motor Function Classification System.

experienced adverse events of vomiting; no patients taking placebo experienced adverse events of retching.

In the OLE phase, the mean number of daily sprays administered was 6.56 (SD 3.04), with a maximum of 10.5 over the duration of the OLE phase. In the active-to-active group (n=43), the mean number of daily sprays administered was 7.01 (SD 3.04). In the placebo-to-active group (n=24), the mean number of daily sprays administered was 5.75 (SD 2.93). Three patients withdrew from the OLE phase because of adverse events of retching/vomiting, seven more reported vomiting as an adverse event, and two more reported retching as an adverse event.

Safety

Overall, the reported adverse events in both treatment groups were generally mild or moderate in severity (Table 2). The rates of treatment-emergent serious adverse events (SAEs) was slightly higher in the placebo group (12%) than in the nabiximols group (9%) during the randomized phase.

Overall, four patients experienced SAEs in the nabiximols group. Two patients experienced SAEs of change in seizure profile (convulsion and grand mal convulsion), one experienced food aversion and retching, and one experienced viral upper respiratory tract infection.

Overall, three patients experienced SAEs in the placebo group. One patient each experienced a SAE of change in seizure profile (partial seizures), lower respiratory tract infection, and shunt malfunction.

Two patients discontinued nabiximols treatment because of adverse events during the randomized phase compared with no patients in the placebo arm. Discontinuation was because of retching for one patient (who was withdrawn at the end of treatment) and oropharyngeal pain, stomatitis, and lower respiratory tract infection for the other (who was withdrawn 24d into the treatment period).

One patient taking nabiximols experienced an adverse event of hallucination on Day 47 of treatment that was considered mild and non-serious by the investigator, and which resolved 23d later with no action taken. The patient had no history of psychiatric disorders and was taking six sprays per day at the time of the event.

No abnormalities associated with either treatment were noted in laboratory data, including liver function tests, and vital signs in either trial phase.

Thirty-seven (51%) patients had an antecedent history of epilepsy. Improvement in the rates of frequency and duration of seizure events were observed in several patients, including one in the nabiximols arm whose daily seizure events disappeared altogether under treatment. One child in the placebo arm had reported 'partial seizures' as a SAE.

In total, 19 (28%) patients experienced at least one SAE in the OLE phase, and nine (13%) patients discontinued nabiximols because of adverse events. Discontinuation rates were higher in the placebo-to-active arm (six [25%] patients) in comparison to the active-to-active arm (three [7%] patients). Of the patients who discontinued treatment due to adverse events in the OLE, six had psychiatric adverse events, the most common of which involved two (3%) patients with low mood and two (3%) with hallucinations. Five patients had gastrointestinal adverse events leading to discontinuation, the most common was vomiting in two (3%) patients. The remaining adverse events leading to discontinuation were observed as single patient occurrences. As described above, two patients experienced hallucinations in the OLE part of the trial. Both patients received placebo in the randomized trial phase. One of these cases was considered significant as an SAE and was associated with a suicide attempt after 114d of nabiximols dosing (linked with auditory hallucinations) at the end of the trial. The patient had somnolence, increased anxiety, and low mood preceding the event which led to a dose reduction of three sprays per day and subsequently discontinuation of treatment. A psychiatric evaluation considered the increased levels of anxiety secondary to little improvement in functional disability.

Table 2: Summary of treatment-emergent adverse events affecting more than two patients in either treatment group; randomized phase (safety set)

Preferred term	Nabiximols (n=47)	Placebo (n=25)
All patients with at least one treatment-emergent adverse events	39 (83.0)	23 (92.0)
Retching	6 (12.8)	0
Vomiting	6 (12.8)	4 (16.0)
Constipation	1 (2.1)	3 (12.0)
Pyrexia	3 (6.4)	2 (8.0)
Gastroenteritis	4 (8.5)	3 (12.0)
Lower respiratory tract infection	4 (8.5)	3 (12.0)
Upper respiratory tract infection	4 (8.5)	3 (12.0)
Nasopharyngitis	4 (8.5)	1 (4.0)
Somnolence	6 (12.8)	2 (8.0)
Convulsion	3 (6.4)	2 (8.0)
Poor quality sleep	3 (6.4)	1 (4.0)

Data are n (%).

Efficacy

Overall, no difference was noted in the primary endpoint of caregiver-reported spasticity 0 to 10 NRS score between the nabiximols and placebo groups (Fig. 1). For the intention to treat analysis set, the least square mean difference between the nabiximols and placebo arms for change in spasticity 0 to 10 NRS score was −0.166 (95% confidence interval [CI] −1.119 to 0.787; p=0.7291) (Table 3). Caregiver-reported spasticity 0 to 10 NRS scores during the OLE phase are presented in Figure 2.

Numerical improvements in secondary outcome measures that were not quite statistically significant were noted for sleep 0 to 10 NRS and MTS scores (Table 4).

DISCUSSION

There has recently been considerable peer review on spasticity in childhood movement disorders and what exactly is

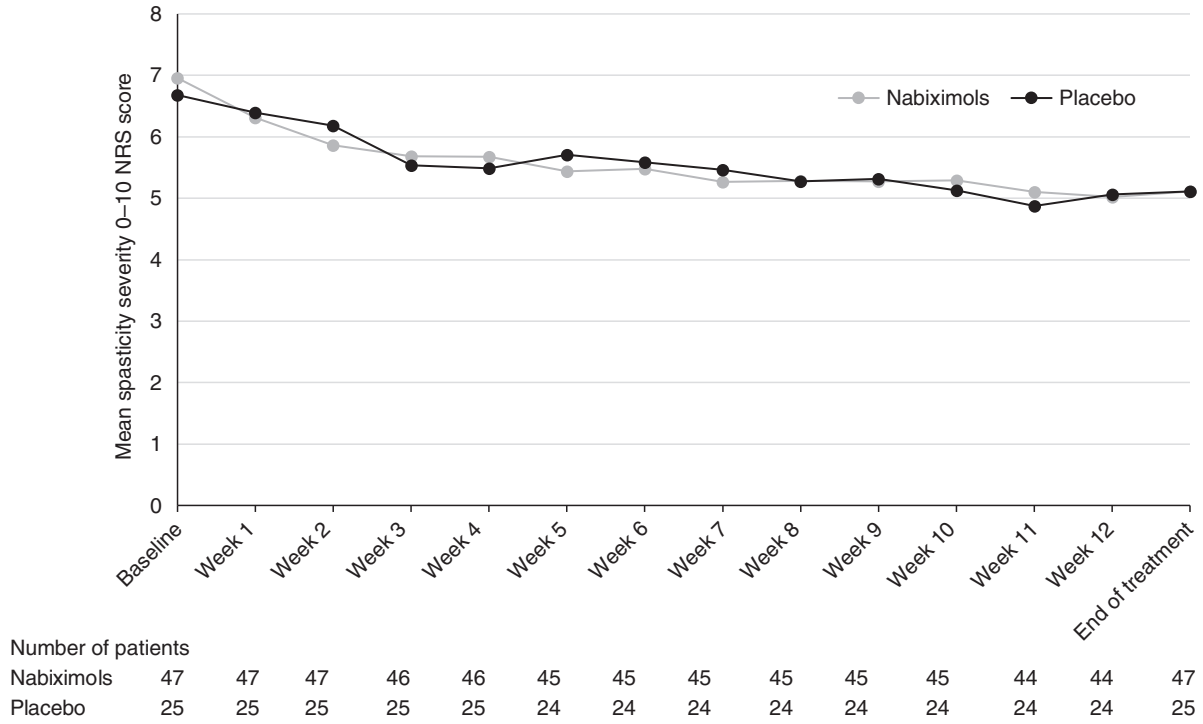

Figure 1: Summary of spasticity severity 0 to 10 Numerical Rating Scale (NRS) score by week; randomized phase (intention to treat set).

Table 3: Analysis of change from baseline to the end of treatment in spasticity severity 0 to 10 Numerical Rating Scale (NRS) score; randomized phase (intention to treat set)

Time point	Nabiximols (*n*=47)	Placebo (*n*=25)
Baseline	6.96 (1.39)	6.68 (1.39)
End of trial	5.11 (2.10)	5.11 (2.05)
Change from baseline	−1.85 (1.93)	−1.57 (2.10)
Parameter		
Least squares mean (SE)[a]	−1.812 (0.281)	−1.645 (0.385)
95% CI[a]	−2.371 to −1.252	−2.414 to −0.877
Treatment difference (nabiximols vs placebo)	−0.166 (0.478)	
95% CI	−1.119 to 0.787	
p	0.729	

[a]Analysed using analysis of covariance for change from baseline in spasticity severity 0 to 10 NRS score at the end of treatment, with baseline score as a covariate and treatment as fixed effect. SD, standard deviation; SE, standard error; CI, confidence interval.

meant by the term.[23,24] The clinical and biomechanical concepts of velocity-dependent, elastic muscle rigidity are potential targets for treatments that improve function, participation, and quality of life. The pathophysiology of how this occurs, or how any relevant motor features are observed, is generally poorly defined.

The National Institute for Health and Care Excellence guideline CG145, 'spasticity in under 19s: management', reviewed the evidence base on all potential pharmacological options,[25] highlighting the lack of moderate or high grade clinical trial evidence to support the use of any oral treatment to reduce or modify muscle tone in paediatric populations, including baclofen, benzodiazepines (as well as diazepam), dantrolene, clonidine, and other movement modifying agents such as trihexyphenidyl and tetrabenazine. There is evidence on the use of botulinum neurotoxin A to treat focal spasticity in patients experiencing postural, functional, or quality of life difficulties including pain and sleep disturbance.[25]

To date, there is only a limited evidence base into the use of cannabinoids to reduce muscle tone in children.[6] This multicentre double-blind, randomized, placebo-controlled trial evaluated the effect of nabiximols on non-progressive spasticity in the paediatric population. A variety of standardized measures were used to explore the complex issue of spasticity and movement disorder, and how any change in muscle tone is functionally relevant for the individual child and their family.

As such, the trial was designed to minimize bias and potential confounders. Analysis was performed only on individuals who did not alter their background treatment. As with all adult and paediatric trials evaluating treatment options in spasticity, it is challenging to find an effective, reproducible comparator other than placebo in addition to stable background medication. The objective clinical assessments of muscle tone, MTS and MAS, can show inter- and intraobserver variability,[26,27] but they are widely used endpoints in all adult and paediatric trials of symptomatic treatment of spasticity.

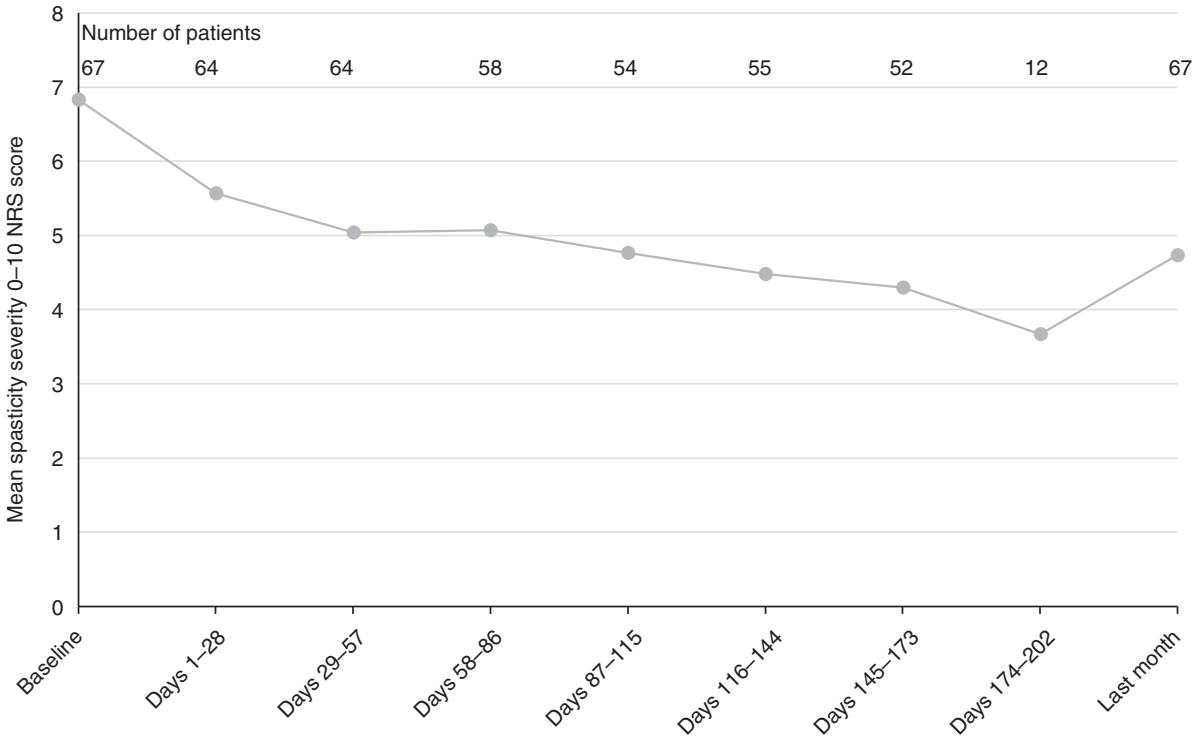

Figure 2: Summary of spasticity severity 0 to 10 Numerical Rating Scale (NRS) score by week; open-label extension (OLE) phase, all patients received nabiximols. Baseline for patients in the OLE phase is their prerandomized phase baseline.

Table 4: Summary of secondary endpoints; randomized phase (intention to treat set)

Endpoint	Nabiximols[a] (*n*=47)	Placebo (*n*=25)	Treatment difference[b] (95% CI)	*p*
Sleep 0–10 NRS	−1.38 (1.85)	−0.848 (1.36)	−0.324 (−1.03 to 0.382)	0.363
MTS[c]	−5.20 (26.31)	−4.61 (21.35)	−4.68 (−16.40 to 7.05)	0.428
MAS[d]	−10.67 (11.98)	−10.72 (13.46)	−0.66 (−6.39 to 5.08)	0.820
CP QoL	0.784 (7.33)	1.47 (9.39)	−1.07 (−5.44 to 3.31)	0.627
PPP (pain most troublesome)	−17.9 (14.28)	−19.9 (13.83)	4.9 (−0.6 to 10.4)	0.079
PPP (pain second most troublesome)	−9.3 (11.80)	−16.8 (15.32)	8.4 (1.4–15.4)	0.021
Comfort questionnaire	−0.132 (104.1)	−12.49 (64.68)	0.378 (−1.93 to 2.69)	0.745

Data are mean (SD) unless otherwise stated. Negative treatment differences favour the nabiximols treatment group. [a]Change from baseline to the end of treatment. [b]Calculated by analysis of covariance; difference between nabiximols vs placebo. [c]Maximum muscle reading. [d]All muscles recorded combined. SD, standard deviation; CI, confidence interval; NRS, Numerical Rating Scale; MTS, Modified Tardieu Scale; MAS, Modified Ashworth Scale; CP QoL, Cerebral Palsy Quality of Life – Child/Teen Questionnaire; PPP, Paediatric Pain Profile.

The primary endpoint of this trial was set by the Paediatric Committee of the European Medicines Agency to resemble the endpoint in the adult trials of nabiximols in patients with multiple sclerosis and spasticity. The spasticity 0 to 10 NRS was adopted as a caregiver-reported measure of how 'stiff' the carer felt the child was. Several secondary endpoints were also recorded to objectively measure muscle tone at the time of all clinical visits (MAS and MTS), as well as other validated assessments of pain, sleep quality, behaviour, and quality of life. Of note, nabiximols did not consistently differentiate from placebo for change in MAS score from baseline in adult patients with spasticity due to multiple sclerosis, even if the two treatments separated for change in average spasticity 0 to 10 NRS score.[10,14]

The results of the randomized phase showed no difference in tolerability of the oromucosal spray between the active and placebo arms. However, many of the children found the formulations relatively unpalatable. The side effect profile was similar between the two treatment groups in the randomized phase, with most of the adverse events observed as mild to moderate in severity. Two patients were withdrawn due to adverse events in the nabiximols arm compared with none for placebo. Retching was observed in 12.8% of patients in the nabiximols group compared to none for placebo. During the randomized phase, four (9%) patients experienced SAEs in the nabiximols group and three (12%) patients experienced SAEs in the placebo group. In the OLE phase, the overall incidence

of SAEs was higher than for patients taking nabiximols in the randomized phase (9% in the randomized phase vs 28% in the OLE phase). This was possibly because of the longer treatment duration in the OLE phase (24wks vs 12wks).

Ensuring safety of medicinal products and methodological rigour in any trial involving children is paramount. The main concern for everyone involved in the design and delivery of the trial was the potential psychoactive side effect of cannabinoids, particularly THC, in the paediatric and adolescent population. The trial design included clear exclusion criteria for history of schizophrenia or other psychotic illness in the young person or first-degree relative, and the trial proceeded with extreme caution. One patient in the randomized phase reported mild hallucinations compared to no patients on placebo, and two patients in the OLE also developed hallucinations. As noted above, one of these (auditory hallucinations) was associated with a suicide attempt.

Interestingly in this trial, no abnormalities associated with nabiximols use were noted in liver function tests. This contrasts with CBD use alone in paediatric patients with epilepsy, which has been associated with elevations in liver transaminases.[28]

This trial provided no evidence of efficacy for nabiximols to reduce spasticity in an overall population of children and young people with cerebral palsy or static post-traumatic CNS injury.

In the UK, children aged 8 years or older receive much less multidisciplinary input compared with preschool-age children. During the trial, support for the child and family was provided by a full multidisciplinary team including a physiotherapist and paediatrician specialized in movement disorder. The marked improvement seen in both the placebo and nabiximols arms during the randomized phase could potentially be associated with this increased support for children enrolled at UK sites (total 85% of patients), as part of a 'placebo' effect. As such, the outcome of this trial reiterates the importance of clinical support for children with complex disability outlined in both National Institute for Health and Care Excellence guidelines CG145 (spasticity) and NG62 (cerebral palsy).[25,29]

Limitations

The primary endpoint of caregiver-reported spasticity 0 to 10 NRS relied on the primary caregiver reporting daily. The use of this daily caregiver assessment as the primary endpoint is, however, a limitation of this trial and most other paediatric trials. The spasticity 0 to 10 NRS was originally validated as a self-report measure for adults.[30] As such, it is a largely subjective measure which is distinct from the assessment of any cardinal features of spasticity, such as increased muscle tone, which can be rated more appropriately by a trained health care professional. Conversely, as stated above, the MTS and MAS assessments are subject to inter- and intraobserver variability.[26,27] An investigation of the reliability of the MAS to measure spasticity in children showed significant deficiencies and suggested that data generated from MAS relating to spasticity should be regarded with a degree of caution.[26] In consideration of this, measures adopted in this trial included site training to reduce the interobserver variability, and the use of the same examiner each time (whenever possible) to reduce the intraobserver variability. In this study, staff at investigational sites administering the MAS and MTS assessments could be involved in other study procedures such as the collection of adverse events and, as such, did not qualify as 'independent' raters. We cannot rule out that this involvement of raters in the management of patients could have informed MAS and MTS assessments. This trial was conducted in a medically very complex group of children with multiple underlying comorbidities, often with severe learning disabilities, behavioural problems, and on multiple medications. As a result, the adverse events reported are also frequently observed in the wider subpopulation and could have confounded the assessment of beneficial effects.

CONCLUSION

After 12 weeks of treatment, paediatric patients treated with nabiximols did not experience statistically significant improvements in spasticity compared with placebo-treated patients. Any improvements in secondary outcome measures also did not reach statistical significance. Compared to the established safety profile of nabiximols in adults with multiple sclerosis and chronic pain, there was no new safety signal detected. Three cases of hallucinations were observed in this cohort. It is possible that patients with cerebral palsy may have increased susceptibility to neuropsychiatric adverse drug effects; however, this study was not designed to demonstrate this.

ACKNOWLEDGEMENTS

The authors would like to thank the patients who took part in the trial, as well as the staff that assisted with the trial at each site. The authors would also like to acknowledge and thank Helen J Dean BSc (Hons) of GW Research Ltd for her contributions to the management of the trial. Finally, the authors would like to thank the 08258 study group. The members of the 08258 study group are as follows: Nick Brown, Salisbury NHS Foundation Trust, Salisbury District Hospital, Salisbury, UK; Lucinda Carr, Great Ormond Street Hospital Foundation Trust, London, UK; Aviva Fattal-Valevski, Dana Children's Hospital, Tel Aviv Sourasky Medical Centre, Tel Aviv, Israel; Mary Gainsborough, Sirona Care & Health, Bristol, UK; Dafna Guttman, The Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Ramat Gan, Israel; Josef Kraus, Klinika detske neurologie 2. LF UK a FN Motol, Praha 5, Czech Republic; Katherine R Martin, Nottingham Children's Hospital, Nottingham University Hospitals NHS Trust, Nottingham, UK; Santosh Mordekar, Sheffield Children's NHS Foundation Trust, Sheffield, UK; Valerie Orr, Royal Hospital for Children Glasgow, Glasgow, UK; Alison Sansome, Cambridge Community Services, Community Child Health, Cambridge, UK; Sarah

Steel, Norfolk and Norwich University Hospitals NHS Foundation Trust, Norwich, UK; Richard Tomlinson, Royal Devon & Exeter NHS Foundation Trust, Exeter, UK; Tong Hong Yeo, Royal Hospital for Children Glasgow, Glasgow, UK; William P Whitehouse, Nottingham Children's Hospital, Nottingham University Hospitals NHS Trust, Nottingham, UK. And the safety review team: Alasdair Parker, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK; Neil Wimalasundera, Great Ormond Street Hospital Foundation Trust, London, UK. This trial was sponsored by GW Research Ltd. Bola Tayo and Daniel Checketts are employees of GW Research Ltd and own shares in GW Pharmaceuticals Plc. Charlie Fairhurst and Susie Turner have served as investigators on a single GW clinical trial each; Ram Kumar has served as an investigator on multiple GW trials. There were no direct or indirect financial gains for investigators.

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EFICACIA Y SEGURIDAD DE CANNABINOIDES NABIXIMOL PARA EL MANEJO DE LA ESPASTICIDAD EN PACIENTES PEDIÁTRICOS CON PARÁLISIS CEREBRAL O LESIÓN CEREBRAL TRAUMÁTICA: UN ENSAYO CONTROLADO ALEATORIO

OBJETIVO

Evaluar la eficacia, seguridad y tolerabilidad del cannabinoides nabiximol de aplicación en spray bucal como terapia complementaria para niños con espasticidad debido a parálisis cerebral o lesión traumática del sistema nervioso central que no responden al tratamiento convencional.

MÉTODO

En total, 72 pacientes (media [DE] edad 12 años 4 meses [3 años 1 mes], rango 8-18 años) fueron aleatorizados en una proporción de 2: 1 para recibir nabiximol spray (n = 47; 29 masculinos, 18 femeninos) o placebo (n = 25; 15 masculinos, 10 femeninos) durante 12 semanas (12 aplicaciones de spray / día máx basados en la respuesta clínica / tolerabilidad). El resultado primario fue el cambio en el nivel basal de espasticidad en una Escala de Calificación Numérica (NRS) de 0 a 10, evaluada por el cuidador primario a las 12 semanas. Los resultados secundarios incluyeron medidas adicionales para la espasticidad, la calidad del sueño, el dolor, la calidad de vida relacionada con la salud, el confort, la depresión y la seguridad.

RESULTADOS

No hubo diferencias significativas en la espasticidad de 0 a 10 NRS entre los grupos de que recibieron nabiximol versus el grupo placebo después de 12 semanas. No se observaron diferencias estadísticamente significativas para ningún criterio de valoración secundario. Los eventos adversos fueron predominantemente leves o moderados en severidad; sin embargo, se informaron tres casos de alucinaciones.

INTERPRETACIÓN

El nabiximol fue generalmente bien tolerado; sin embargo, se observaron eventos adversos neuropsiquiátricos. No se observó una reducción significativa en la espasticidad con el tratamiento con nabiximoles versus placebo.

EFICÁCIA E SEGURANÇA DO MEDICAMENTO NABIXIMOLS CANABINÓIDE PARA ESPASTICIDADE PEDIÁTRICA EM PARALISIA CEREBRAL OU LESÃO CEREBRAL TRAUMÁTICA: UM ESTUDO CLÍNICO RANDOMIZADO

OBJETIVO

Avaliar a eficácia, segurança e tolerabilidade do medicamento oromucosal nabiximols canabinóide como terapia adjunta para crianças com espasticidade devida a paralisia cerebral/lesão traumática do sistema nervoso central com resposta inadequada a tratamentos existentes.

MÉTODO

Em geral, 72 pacientes (média [DP] idade 12a 4m [3a 1m], variação 8–18a) foram randomizados em uma taxa de 2:1 para receber nabiximols (*n*=47; 29 sexo masculino, 18 sexo feminino) ou placebo (*n*=25; 15 sexo masculino, 10 sexo feminino) por 12 semanas (12 sprays/dia máx. com base na resposta clínica/tolerabilidade). O resultado primário foi mudança com relação a linha de base no nível de espasticidade um uma Escala Numérica de Pontuação (ENP) de 0 a 10, avaliada pelo cuidador primário com 12 semanas. Resultados secundários incluíram medidas adicionais de espasticidade, qualidade do sono, dor, qualidade de vida relacionada à saúde, conforto, depressão, e segurança.

RESULTADOS

Não houve diferença significativa na espasticidade Segundo a ENP 0 a 10 entre os grupos nabiximols versus placebo após 12 semanas. Nenhuma diferença estatisticamente significativa foi observada para nenhum desfecho secundário. Eventos adversos foram predominantemente leves ou moderados em severidade; no entanto, três casos de alucinações foram reportados.

INTERPRETAÇÃO

Nabiximols foi em geral bem tolerado; no entanto eventos adversos neuropsiquiátricos foram observados. Nenhuma redução significativa na espasticidade com o tratamento com nabiximols versus placebo foi observada.