Safety and efficacy of nabiximols on spasticity symptoms in patients with motor neuron disease (CANALS): a multicentre, double-blind, randomised, placebo-controlled, phase 2 trial

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Summary

Background Spasticity is a major determinant of disability and decline in quality of life in patients with motor neuron disease. Cannabinoids have been approved for symptomatic treatment of spasticity in multiple sclerosis. We investigated whether cannabinoids might also reduce spasticity in patients with motor neuron disease.

Methods We did an investigator-initiated, randomised, double-blind, placebo-controlled, phase 2 clinical trial at four tertiary motor neuron disease centres in Italy. Eligible patients were aged 18–80 years; had possible, laboratory-supported probable, probable, or definite amyotrophic lateral sclerosis as defined by revised El Escorial criteria, or primary lateral sclerosis according to Pringle's criteria; had spasticity symptoms due to motor neuron disease for at least 3 months; had spasticity scores of 1 or greater in at least two muscle groups on the Modified Ashworth Scale; and were taking an antispasticity regimen that was maintained at a stable dose for 30 days before enrolment. Participants were assigned (1:1) by an independent statistician via a computer-generated randomisation sequence to a standardised oromucosal spray (nabiximols) containing a defined combination of delta-9-tetrahydrocannabinol and cannabidiol (each 100 µL actuation contained 2·7 mg delta-9-tetrahydrocannabinol and 2·5 mg cannabidiol) or to placebo for 6 weeks. Participants self-titrated during the first 14 treatment days according to a predefined escalation scheme (maximum 12 actuations per 24 h), then maintained that dose for 4 weeks. The primary endpoint was the change in the score on the Modified Ashworth Scale, which was assessed at baseline and after 6 weeks. Safety and tolerability were also monitored. Participants, investigators, site personnel, and the study statistician were masked to treatment allocation. All randomised participants who received at least one dose of study drug were included in the analysis. This trial is registered with ClinicalTrials.gov, number NCT01776970. The trial is closed to new participants with follow-up completed.

Findings Between Jan 19, 2013, and Dec 15, 2014, 60 participants were randomly assigned, and 59 participants were included in the final analysis (29 in the nabiximols group and 30 in the placebo group). Modified Ashworth Scale scores improved by a mean of 0·11 (SD 0·48) in the nabiximols group and deteriorated by a mean of 0·16 (0·47) in the placebo group (adjusted effect estimate –0·32 [95% CI –0·57 to –0·069]; p=0·013). Nabiximols was well tolerated, and no participants withdrew from the double-blind phase of the study. No serious adverse effects occurred.

Interpretation In this proof-of-concept trial, nabiximols had a positive effect on spasticity symptoms in patients with motor neuron disease and had an acceptable safety and tolerability profile. These findings should be investigated further in larger clinical trials.

Funding Italian Research Foundation for Amyotrophic Lateral Sclerosis.

Lancet Neurol 2018

Published Online
December 13, 2018
http://dx.doi.org/10.1016/S1474-4422(18)30406-X

See Online/Comment
http://dx.doi.org/10.1016/S1474-4422(18)30493-9

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Introduction

The clinical spectrum of motor neuron disease encompasses extremely heterogeneous phenotypes, including amyotrophic lateral sclerosis, which is the most common and severe form and involves both lower and upper motor neurons, primary lateral sclerosis, which is characterised by pure or predominant degeneration of upper motor neurons, and progressive muscular atrophy, which is defined by selective involvement of lower motor neurons.[1–3] Available neuroprotective treatments only moderately reduce the rate of disease progression. Therefore, in the absence of a cure, symptom control to maintain quality of life is the cornerstone of management of patients with motor neuron diseases.[1]

Spasticity is characterised by velocity-dependent increases in muscle tone in response to an externally imposed stretch or during voluntary movement, and develops as a result of degradation of upper motor neurons.[4] It can cause substantial disability in patients, reduce quality of life, and potentially result in a chain of secondary complications, such as muscle fibrosis, joint contractures, muscle cramps or spasms, and pain.[5,6] Spasticity is one of the defining characteristics of primary lateral sclerosis. It occurs to a variable degree in

Research in context

Evidence before this study

We searched PubMed, MEDLINE, and the Cochrane Database of Systematic Reviews with the terms "motor neuron disease" OR "amyotrophic lateral sclerosis" AND "spasticity" OR "cannabinoids" without any language restrictions for articles published up to Feb 6, 2018. Despite clinical practice guidelines that recommend different pharmacological approaches, evidence to support treatment of spasticity in motor neuron disease is scant. Notably, a Cochrane review of treatments for spasticity in amyotrophic lateral sclerosis and motor neuron disease published in 2012 identified only one randomised controlled trial of moderate-intensity endurance-type exercise versus usual activities in 25 patients with amyotrophic lateral sclerosis. The Cochrane authors concluded that that trial was too small to establish whether individualised exercises had either beneficial or harmful effects, and that further research was thus needed. Since then, however, no other medical, surgical, or alternative treatment for spasticity has been assessed in a randomised fashion in this patient population. A small randomised double-blind, crossover study investigated the effect of orally administered delta-9-tetrahydrocannabinol on cramps in patients with amyotrophic lateral sclerosis. Although the drug was well tolerated, subjective improvements in cramp symptoms were not reported. Several clinical studies have shown the safety and efficacy of cannabinoids in the control of spasticity in people with multiple sclerosis. Furthermore, the positive effects of cannabinoids on pain emerged in various conditions, and pain is a frequent complaint of patients with motor neuron disease. Preclinical studies done in the SOD1-G93A transgenic mouse model support the hypothesis that cannabinoids could not only exert an antispastic effect, but also be beneficial as neuroprotective agents in amyotrophic lateral sclerosis.

Added value of this study

Our study, to our knowledge, is the first randomised controlled trial of the safety and efficacy of a pharmacological treatment for spasticity in motor neuron disease and the first trial of a combination of tetrahydrocannabinol and cannabidiol (nabiximols) in motor neuron disease. We provide preliminary evidence of efficacy compared with placebo in controlling spasticity (as shown by significant improvements in scores on the Modified Ashworth Scale at 6 weeks), with some evidence of an additional beneficial effect on pain, in patients with motor neuron disease. Treatment with nabiximols was well tolerated and was not associated with any serious adverse effects.

Implications of all the available evidence

Although nabiximols has been licensed in many countries for symptomatic control of spasticity in multiple sclerosis and cannabinoids are increasingly recognised as a valuable option for management of cancer, neuropathic, and non-neurophatic pain, further confirmatory phase 3 studies are warranted to confirm our findings, and more clinical research into the potential neuroprotective effect of cannabinoids in slowing disease progression in motor neuron disease is warranted.

patients with amyotrophic lateral sclerosis, but seems more frequent in patients presenting with a predominant upper motor neuron phenotype,[3] although epidemiological data both at presentation and during disease progression are scarce.[2,4,6,7] Although spasticity is an important and potentially treatable condition, evidence is insufficient to recommend drugs or non-pharmacological interventions to treat it in patients with motor neuron disease.[1,5,6] Furthermore, available antispasticity drugs can be associated with increased muscle weakness or fatigue, which are particularly undesirable side-effects in these patients.[5] Although baclofen, dantrolene, benzodiazepines, gabapentin, and levetiracetam have been reported to reduce spasticity in some patients with amyotrophic lateral sclerosis, they have not been adequately tested.[5] The one small clinical trial[8] done was not sufficient to establish whether moderate-intensity endurance exercise was either beneficial or harmful for the treatment of spasticity in amyotrophic lateral sclerosis.[5]

In the past decade, several clinical studies[9–14] have shown the safety and efficacy of cannabinoids in the control of spasticity in people with multiple sclerosis. Preliminary reports suggest that cannabinoids could alleviate some of the symptoms associated with motor neuron disease, such as muscle spasms, sialorrhoea, pain, spasticity, and depression, and could improve patients' appetites.[15–17] In a small randomised, double-blind, crossover study[18] published in 2010, the effect of tetrahydrocannabinol (THC) on cramps in patients with amyotrophic lateral sclerosis was investigated. Although the drug was well tolerated, subjective improvement was not noted. The effects of cannabinoids are mediated via specific cell membrane receptors, CB1 and CB2, and include not only muscle relaxation, but also appetite stimulation and potential analgesic, antiemetic, anticonvulsant, anxiolytic, anti-inflammatory, antioxidant, and neuroprotective effects.[11,19,20] Studies[21–24] done in the SOD1-G93A transgenic mouse model of amyotrophic lateral sclerosis showed that cannabinoids could delay motor impairment and prolong murine survival. A post-mortem study[25] showed that the number of cannabinoid receptors is increased in the motor cortices of patients with motor neuron disease compared with that in the motor cortices of people without motor neuron disease. The aim of our proof-of-concept study was to explore the safety and effects of a standardised oromucosal spray (nabiximols) containing a defined combination of THC and cannabidiol on spasticity related to motor neuron disease.

Methods

Study design and participants

The Cannabis Sativa Extract in Amyotrophic Lateral Sclerosis and other Motor Neuron Disease (CANALS) study was an investigator-initiated, randomised, double-blind, placebo-controlled, parallel-group, phase 2 clinical trial at four tertiary centres for motor neuron disease in Italy: the Department of Neurology, Institute of Experimental Neurology, IRCCS San Raffaele Scientific Institute (Milan, Italy); Amyloid Lateral Scleroris Centre, Istituti Clinici Scientifici Maugeri, IRCCS (Milan, Italy); Neuromuscular Centre, University of Padova (Padua, Italy); and NeuroMuscular Omnicentre (Milan, Italy). The trial was organised by the Institute of Experimental Neurology. Eligible participants were aged 18–80 years; had possible, laboratory-supported probable, probable, or definite amyotrophic lateral sclerosis as defined by revised El Escorial criteria,[4] or primary lateral sclerosis according to Pringle's criteria;[2] had a spasticity score of 1 or greater on the five-point Modified Ashworth Scale (MAS) in two or more muscle groups; had spasticity due to motor neuron disease for at least 3 months that was incompletely controlled by therapy; were taking an antispasticity regimen that was maintained at a stable dose for 30 days before enrolment and throughout the study; and had optimised and not altered any physiotherapy regimen or medication likely to affect spasticity in the 3 weeks before start of treatment, and self-judged spasticity to be a relevant cause of movement impairment. Key exclusion criteria were any concomitant conditions that had spasticity-like symptoms or that might affect spasticity, use of cannabis or cannabinoid-based medications in the 30 days before study entry, administration of botulinum toxin during the preceding 6 months, concurrent history of significant psychiatric, renal, hepatic, cardiovascular, or convulsive disorders, cognitive impairment, fixed-tendon contractures, known or suspected history of alcohol or substance misuse, and being bedridden or tracheotomised. The full list of exclusion criteria is in the appendix. Central and local ethics committees approved the study. All participants provided written informed consent before inclusion.

Randomisation and masking

Participants were enrolled in the study by trial investigators. A week after a baseline assessment, consecutive patients fulfilling the eligibility criteria were randomly assigned (1:1) to either active treatment or placebo. Randomisation was done centrally according to an allocation schedule with balanced randomly permuted blocks of four via a computer-based algorithm to a consecutive series of numbers by an independent statistician, who had no other role in the study or in data analysis. Participants were assigned to groups consecutively by study investigators acccording to the allocation schedule. All participants, investigators, site personnel, steering committee members, and the study statistician were masked to the treatment allocation. Vials and boxes were prepared centrally (GW Pharma, Cambridge, UK) and had standardised labelling to ensure maintenance of blinding. Although accidental unmasking was not formally tested, the active treatment and placebo solutions were transparent and indistinguishable.[9,13,14,26] The treatment allocation code was kept in a sealed opaque envelope. Participants were instructed not to disclose potential symptoms related to their treatment regimen to the examining neurologist. Assessment of outcome measures was done before any safety or tolerability assessments.

Procedures

After screening, at which eligibility for inclusion was assessed, eligible patients entered a 7-day baseline period, during which they were required to complete a diary recording of their daily spasticity levels, pain, spasm frequency, and sleep disruption on a ten-point numeric rating scale. They then returned to the study site for visit two and, after eligibility was reconfirmed, were randomly assigned to either nabiximols or placebo. Nabiximols was delivered via a highly standardised pump action oromucosal spray. Each 100 µL actuation delivered 2·7 mg delta-9-THC and 2·5 mg cannabidiol in a 50:50 solution of ethanol and propylene glycol. Participants were instructed to self-titrate during the first 14 treatment days according to a predefined escalation scheme to their optimal dose, up to a maximum of 12 actuations in 24 h, with the aim of balancing symptom relief and unwanted effects. If any tolerable side-effects occurred, patients were advised not to increase the dose; if intolerable side-effects occurred, dose reduction was advised.[9–14,26] After initial titration, participants were asked not to modify daily dosing. Spasticity, pain, spasm frequency, and sleep numeric rating scales and dosing diaries were completed daily. 3 weeks after randomisation, investigators contacted participants by phone to monitor compliance and safety. Participants attended an end-of-study visit 4 weeks after the fixed dose had been established (ie, 6 weeks after randomisation). Subsequently, all patients in both groups who completed this phase of the trial were given the opportunity to enrol in a 6-week open-label extension study, during which all participants received nabiximols. A 2-week titration period was necessary for participants in the placebo group, which was then followed by 4 weeks of fixed-dose treatment. Overall, the total trial duration was therefore 13 weeks (ie, 1 week of screening, 2 weeks of intial dose titration, 4 weeks of blinded fixed-dose treatment, and 6 weeks of open-label treatment). Thereafter, patients were followed up according to best clinical practice, and were given the opportunity to continue nabiximols or other cannabinoid-based treatments.

See Online for appendix

Outcomes

The primary outcome was change in scores on the MAS in the active group compared with the placebo group. At

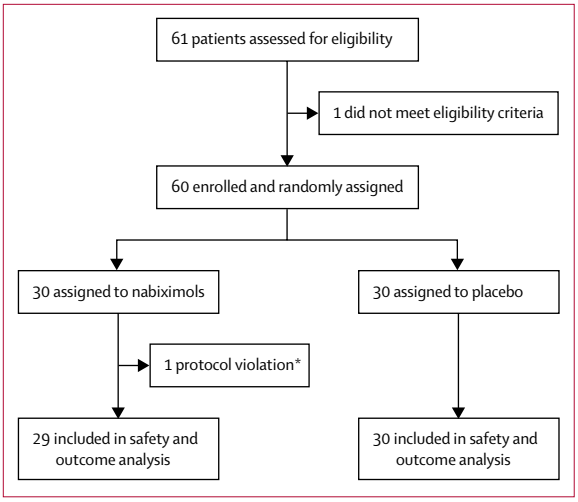

Figure 1: **Trial profile**
A version of the trial profile that includes the open-label phase is presented in the appendix. *Participant moved out of study area, and first administration of nabiximols could not be verified.

	Nabiximols group (n=29)	Placebo group (n=30)
Sex		
Male	18 (62%)	16 (53%)
Female	11 (38%)	14 (47%)
Age, years	58·4 (10·6)	57·2 (13·8)
Diagnosis		
Clinically definite amyotrophic lateral sclerosis	6 (21%)	5 (17%)
Clinically probable amyotrophic lateral sclerosis	4 (14%)	7 (23%)
Laboratory-supported probable amyotrophic lateral sclerosis	3 (10%)	4 (13%)
Clinically possible amyotrophic lateral sclerosis	0 (0%)	1 (3%)
Primary lateral sclerosis	8 (28%)	6 (20%)
Upper-motor-neuron-dominant amyotrophic lateral sclerosis	8 (28%)	7 (23%)
Duration of disease, months	58·6 (33·7)	56·2 (57·5)
Duration of spasticity, months	35·8 (26·3)	43·4 (47·2)
Amyotrophic Lateral Sclerosis Functional Rating Score—Revised*	31·6 (8·0)	31·4 (7·4)
Disease progression rate†	0·5 (0·6)	0·7 (0·7)
Forced vital capacity, maximum % predicted	86·8 (26·8)	81·6 (22·9)
Upper motor neuron score‡	11·5 (2·0)	11·8 (2·2)
Medical Research Council sum score§	92·5 (26·2)	91·3 (23·9)
Ever used cannabis¶	5 (17%)	2 (7%)
Score on Modified Ashworth Scale‖	2·3 (0·6)	2·4 (0·6)
Numeric rating scale spasticity**	5·7 (1·7)	6·1 (1·8)
Numeric rating scale pain**	3·0 (2·5)	3·3 (2·6)
Numeric rating scale spasm frequency**	2·8 (1.8)	3·3 (2·6)
Numeric rating scale sleep disruption**	2·8 (2·4)	3·2 (2·6)
10 m walk, s	50 (60·2)	65·7 (68·0)
Barthel Activities of Daily Living Index††	65·2 (27·4)	54 (23·4)
Body-mass index, kg/m²	25·7 (4·9)	23·9 (3·0)
Gastrostomy	5 (17%)	0 (0%)
Non-invasive ventilation	5 (17%)	3 (10%)

Data are mean (SD) or n (%). *Range 0–48. †Disease progression rate=(48–score on the Amyotrophic Lateral Sclerosis Functional Rating Score—Revised)/disease duration. ‡Range 0–14. §Range 0 (total paralysis) to 120 (normal strength). ¶If patients were using cannabis at the screening visit, they were excluded. ‖Range 0–5. **Range 0–10. ††Range 0–100.

Table 1: **Baseline demographic and clinical characteristics**

randomisation and at the end of the double-blind phase, spasticity scores were calculated for both sides of the body in elbow flexors, extensors, and pronators, wrist and finger flexors, hip adductors and abductors, knee extensors, and foot plantar flexors. A MAS score was then calculated as the sum of the individual scores divided by the number of spastic muscle groups defined at baseline.[27] Participants saw the same assessing neurologist for all tests at all timepoints.

Secondary outcomes, which were measured at baseline and at the end of the double-blind and open-label treatment phases, were patient-reported spasticity, pain, spasm frequency, and sleep scores on the numeric rating scale; timed 10 m walk; scores on the Amyotrophic Lateral Sclerosis Functional Rating Scale—Revised; forced vital capacity; scores on the Barthel Activities of Daily Living Index; body-mass index; and participants', caregivers', and neurologists' global impression of change.[13,14,28,29] Weakness was measured at the end of the double-blind treatment phase with the Medical Research Council sum score (12 muscles per side), and upper motor neuron burden was assessed with the upper motor neuron score, which was calculated by totalling the number of pathological upper motor neuron signs at examination.[30] Safety assessments included monitoring of vital signs, all adverse events (including abnormal findings obtained from oral examination), and use of concomitant drugs at all clinic visits. The primary aim of the open-label study was to enable exploration of safety and tolerability over 3 months.

Statistical analysis

We deemed a difference between groups of 0·25 points or greater on the MAS during the double-blind study phase to be clinically relevant. This value was based on a clinical trial[31] with the same primary outcome that was done in patients with multiple sclerosis. Recruitment of 27 patients per group was estimated to provide a statistical power of 0·8 to detect a difference at a two-sided 0·05 significance level. Assuming a 10% dropout rate, we planned to enrol 60 participants. At the end of the trial, a statistical board, independent from the principal investigator's unit, was appointed to ensure high-quality data entry and analytic processes. The dataset was then cleaned before group imputation and data analysis. The protocol-specified analysis was revised by the independent statistical board and subsequently approved by the

principal investigator's study group before unblinding, on the basis of exploratory assessments of the whole dataset (appendix).

Before statistical analysis, the study population was divided into two groups, according to randomisation assignment. All baseline demographic and clinical characteristics were summarised as absolute numbers and percentages or means and SDs. For the primary endpoint, the change in spasticity was assessed via a linear model (ANCOVA) with age, disease and spasticity duration, and baseline MAS score as the covariate, and treatment group and sex as factors in the model. Data for the Barthel Activities of Daily Living Index, timed 10 m walk, Amyotrophic Lateral Sclerosis Functional Rating Scale—Revised, Medical Research Council score, upper motor neuron score, forced vital capacity, and body-mass index were analysed with the same approach used for the MAS score. For scores on numeric rating scales, the variables for analysis were the mean values recorded during the 1-week baseline period and the last week of both the double-blind and open-label phases. Global impressions of change were analysed with the χ^2 test, with Fisher's correction if necessary. A two-sided significance test was used in all comparisons at the 5% level of significance. All randomly assigned participants who received at least one dose of study medication were included in the analyses (ie, a modified intention-to-treat analysis). Adverse events were coded according to the Medical Dictionary for Regulatory Activities. Because the open-label extension study was non-comparative, no formal statistical analysis for efficacy measures was planned, and the results should be regarded as descriptive only. All analyses were done in Stata (version 12.1). This trial is registered with ClinicalTrials.gov, number NCT01776970.

Role of the funding source

The study funder had no role in study design; data collection, analysis, or interpretation; or writing of the report. The corresponding author and independent statistical board had full access to all study data, and the independent statistical board provided the result to the corresponding author after data analysis was completed. The corresponding author had final responsibility for the decision to submit for publication.

Results

Between Jan 19, 2013, and Dec 15, 2014, 61 participants were enrolled in the study, 60 of whom were randomly assigned (figure 1). One participant moved out of the study area on the day of randomisation, and first administration could not be documented. Therefore, 59 participants were included in our modified intention-to-treat analysis, 29 in the nabiximols group and 30 in the placebo group. Baseline characteristics were well matched between groups, except for the proportion of patients with a gastrostomy (five [17%] in the nabiximols group *vs* none in the placebo group; table 1). The mean MAS score was 2·3 (SD 0·6) in the intervention group and 2·4 (0·6) in the placebo group (table 1). Concomitant

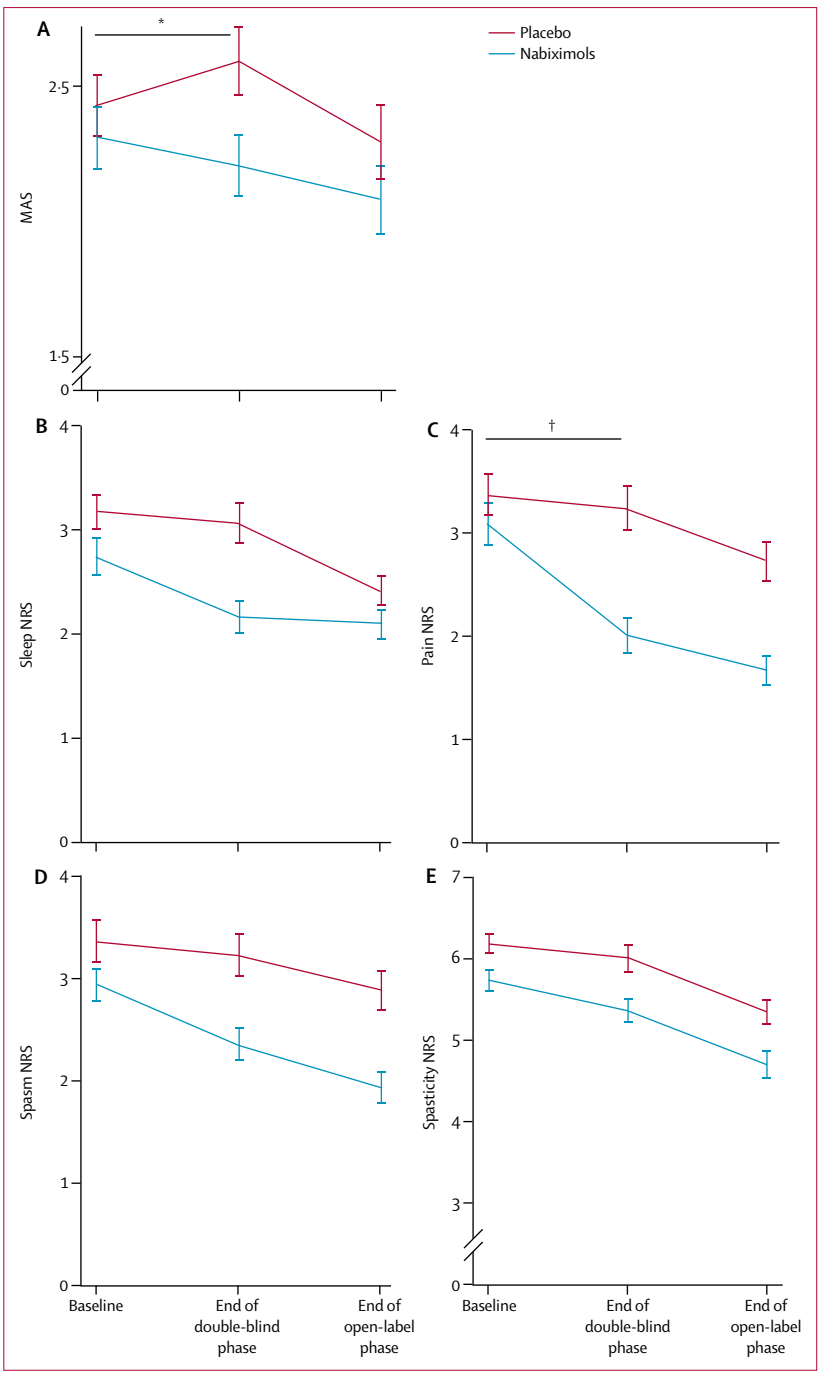

Figure 2: **MAS and NRS scores during the double-blind and open-label phases**
(A) MAS scores (primary outcome); (B) sleep NRS scores; (C) pain NRS scores; (D) spasm NRS scores; (E) spasticity NRS scores. At the end of the double-blind phase, all patients were given the opportunity to enrol in a 6-week open-label extension study, during which all participants received nabiximols. Because the open-label extension study was non-comparative, no formal statistical analysis for efficacy measures was planned, and the results should be interpreted as descriptive only. Error bars represent SDs for the mean values at each timepoint. MAS=Modified Ashworth Scale. NRS=numeric rating scale. *p=0·013 for between-group differences (assessed by ANCOVA). †p=0·017 for between-group differences (assessed by ANCOVA).

	Nabiximols group mean change from baseline (SD; n=29)	Placebo group mean change from baseline (SD; n=30)	Mean effect of treatment* (95% CI)	p value
Modified Ashworth Scale score	–0·11 (0·48)	0·16 (0·47)	–0·32 (–0·57 to –0·07)	0·013
NRS spasticity	–0·32 (2·15)	–0·12 (1·40)	–0·49 (–1·48 to 0·50)	0·324
NRS pain	–0·97 (2·12)	–0·06 (1·47)	–1·15 (–2·10 to –0·21)	0·017
NRS spasm frequency	–0·51 (1·61)	–0·13 (2·02)	–0·71 (–1·68 to 0·27)	0·153
NRS sleep disruption	–0·62 (1·99)	–0·10 (1·90)	–0·79 (–1·80 to 0·22)	0·122
10 m walk, s	–1·48 (33·09)†	–0·53 (30·54)†	0·92 (–17·39 to 19·64)	0·997
Barthel Activities of Daily Living Index	–0·34 (2·97)	–1·00 (7·47)	0·73 (–2·56 to 4·02)	0·660
Forced vital capacity, maximum % predicted	0·57 (9·21)	–6·85 (11·0)	5·38 (–1·09 to 11·85)	0·100
Body-mass index, kg/m²	–0·06 (0·42)	0·06 (0·42)	–0·12 (–0·35 to 0·11)	0·308
Amyotrophic Lateral Sclerosis Functional Rating Score—Revised	–0·10 (1·32)	–0·70 (1·82)	0·62 (–0·22 to 1·48)	0·148
Upper motor neuron score	0·46 (1·50)‡	–0·03 (1·13)	0·41 (–1·48 to 0·50)	0·227
Medical Research Council sum score	–0·79 (8·83)	0·03 (6·14)	–0·73 (–4·94 to 3·49)	0·730
Mean daily actuations§	8·03 (2·9; 1 to 12)	11·2 (1·4; 7 to 12)	..	<0·0001

NRS=numeric rating scale. *β coefficient for mean effect of treatment from ANCOVA model adjusting for the other covariates (ie, baseline assessment for each endpoint, age, sex, disease duration, and duration of spasticity). †Test based on data for 26 participants in the placebo group and 25 in the nabiximols group. ‡Test based on data for 28 participants in the nabiximols group. §Data are mean (SD; range).

Table 2: **Outcome analyses at the end of the double-blind treatment phase**

	Nabiximols group (n=29)	Placebo group (n=30)	p value
Patients' global impression of change	..	..	0·001
Improvement	16 (55%)	4 (13%)	..
Stable	6 (21%)	19 (63%)	..
Deterioration	7 (24%)	7 (23%)	..
Carers' global impression of change	..	..	0·163*
Improvement	7 (24)	2 (7%)	..
Stable	14 (48%)	16 (53%)	..
Deterioration	8 (28%)	12 (40%)	..
Neurologists' global impression of change	..	..	0·080
Improvement	14 (48%)	7 (23%)	..
Stable	11 (38%)	13 (43%)	..
Deterioration	4 (14%)	10 (33%)	..

p values were calculated with the χ^2 test, with Fisher's correction applied in cases in which expected values were less than 5 units. *Fisher's correction applied.

Table 3: **Patients', carers', and neurologists' global impressions of change at the end of the double-blind treatment phase**

antispastic medications were similar between groups at baseline (appendix) and did not change throughout the study.

At the end of the double-blind phase, MAS scores had improved by a mean of 0·11 (SD 0·48) in the nabiximols group and deteriorated by a mean of 0·16 (0·47) in the placebo group (adjusted effect estimate –0·32 [95% CI –0·57 to –0·069]; p=0·013; figure 2, table 2). During the 4-week double-blind phase after dose titration, the mean number of daily actuations was 8·03 (SD 2·9; range 1–12) in the nabiximols group and 11·2 (1·4; 7–12) in the placebo group (p<0·0001; table 2). The mean change in pain scores on the numeric rating scale was –0·97 (SD 2·12) in the nabiximols group and –0·06 (1·47) in the placebo group (adjusted effect estimate –1·15 [95% CI –2·10 to –0·21]; p=0·017; figure 2, table 2; appendix). 16 (55%) of 29 participants in the intervention group rated their global impression of change as improved, compared with four (13%) of 30 in the placebo group (p=0·001 for overall between-group comparison; table 3). No significant between-group differences were noted for caregivers' or physicians' global impressions of change, or for any other secondary outcomes (figure 2, tables 2, 3; appendix).

Nabiximols was well tolerated overall. No participants permanently discontinued treatment during the double-blind phase of the trial. Three patients temporarily discontinued treatment in the nabiximols group, two because of adverse events (one had nausea and anxiety, the other had influenza and experienced an accidental fall) and one because of disease progression. The mean duration of temporary discontinuation was 2·4 days (SD 1·9; range 1–5). No serious adverse events occurred in either group. 22 (76%) participants in the intervention group and eight (27%) in the placebo group had at least one all-cause adverse event, and 21 (72%) and four (13%), respectively, had at least one potentially treatment-related adverse event (table 4; appendix). All these adverse events were mild or moderate in severity. Seven (24%) participants in the nabiximols group had 13 investigator-judged potentially treatment-related adverse events of moderate severity (table 4). One participant in the placebo group had one such adverse event (table 4). The most common adverse events potentially related to nabiximols were asthenia, somnolence, vertigo, and nausea (table 4).

Two patients did not participate in the open-label extension study: one in the nabiximols group who had adverse events and no improvement in symptoms declined to participate, and one in the placebo group was excluded because of a protocol violation (appendix). During the extension phase, three participants who were originally assigned to the nabiximols group withdrew, two because of disease progression and one because of an adverse event related to nabiximols. Four participants who had been assigned to the placebo group discontinued treatment during the open-label phase because of adverse events, three of which were potentially related to nabiximols. 26 patients originally assigned to nabiximols and 28 originally assigned to placebo were available for the end-of-study visit at the end of the open-label phase. During the open-label phase, the mean daily number of actuations significantly decreased to 6·1 (SD 3·4) in patients previously on placebo ($p<0·0001$), but did not change significantly in participants in the intervention group throughout (appendix).

22 participants previously on placebo and 11 assigned to nabiximols throughout the study had at least one potentially treatment-related adverse event during the open-label phase (appendix). There were 22 potentially treatment-related moderate or severe adverse events experienced by 11 participants, nine previously allocated to placebo and two to nabiximols. The most common adverse events potentially related to nabiximols during the open-label phase were asthenia, dizziness, somnolence, vertigo, muscle spasticity or rigidity, and dry mouth (appendix).

MAS scores of participants originally assigned to placebo improved after switching to nabiximols during the extension open-label (mean change –0·28; SD 0·47). We noted a general improvement in efficacy outcome measures for the original placebo group (appendix). Placebo participants' global impression of change improved compared with those recorded during the double-blind phase trial, with 15 (54%) of 28 participants reporting improvements (appendix).

	Nabiximols group (n=29)	Placebo group (n=30)
Any adverse event	22 (76%)	8 (27%)
Any possible, probable, or definite treatment-related adverse event	21 (72%)	4 (13%)
One or more definite treatment-related adverse event	0 (0%)	0 (0%)
Any moderate or severe adverse event	7 (24%)	1 (3%)
Any severe adverse event	0 (0%)	0 (0%)
Any serious adverse event	0 (0%)	0 (0%)
General disorders and administration-site conditions		
Asthenia	7 (24%)	1 (3%)
Malaise	1 (3%)	0 (0%)
Nervous system disorders		
Dizziness	2 (7%)	0 (0%)
Balance disorder	1 (3%)	0 (0%)
Memory impairment	1 (3%)	0 (0%)
Somnolence	5 (17%)	1 (3%)
Syncope	2 (7%)	0 (0%)
Tremors	1 (3%)	0 (0%)
Muscle spasticity	1 (3%)	0 (0%)
Gait disturbance	0 (0%)	0 (0%)
Psychiatric disorders		
Anxiety	1 (3%)	0 (0%)
Agitation	1 (3%)	0 (0%)
Vertigo	5 (17%)	0 (0%)
Vision blurred	1 (3%)	0 (0%)
Palpitations	1 (3%)	0 (0%)
Gastrointestinal disorders		
Dry mouth	1 (3%)	1 (3%)
Nausea	3 (10%)	0 (0%)
Oral pain	1 (3%)	0 (0%)
Oral mucosal disorder	0 (0%)	1 (3%)
Fall	1 (3%)	0 (0%)
Skin and subcutaneous tissue disorders		
Erythema	0 (0%)	1 (3%)
Skin exfoliation	0 (0%)	1 (3%)
Pruritus	0 (0%)	1 (3%)

Data are n (%). Adverse events were judged to be mild, moderate, or severe by investigators. All adverse events were codified on the basis of the Medical Dictionary for Regulatory Activities according to system organ classes. If a participant experienced more than one occurrence of a given adverse event, the participant was counted only once for that adverse event.

Table 4: **Adverse events, including most common potentially treatment-related events**

Discussion

This randomised, double-blind, placebo-controlled, phase 2 trial provides evidence of the efficacy of nabiximols in relieving spasticity in a population of patients with motor neuron disease presenting with overt or predominant involvement of upper motor neurons. The primary endpoint, the MAS score, was significantly improved in the nabiximols group compared with the control group. Although this positive effect on an objective measure of spasticity was complemented by a significant improvement in patients' global impression of change and significant reduction in pain in the nabiximols group compared with the control group, no significant differences were noted between groups for any other secondary endpoints, including sleep quality, spasms, spasticity, strength, upper and lower motor neuron tests, and scores on the Amyotrophic Lateral Sclerosis Functional Rating Scale—Revised. The tolerability problems and adverse events reported in the nabiximols group were modest, with a profile typical of cannabinoids (nausea, dizziness, asthenia, and confusion were common). No patients permanently discontinued treatment during the trial.

Notably, the mean disease duration in our study population was long compared with that in patients with a typical amyotrophic lateral sclerosis phenotype,[3] a finding

consistent with those of previous reports showing an association between long duration of disease and predominant upper motor neuron amyotrophic lateral sclerosis and primary lateral sclerosis.[3] No previous study has specifically addressed the efficacy of cannabinoids as a symptomatic treatment of spasticity in patients with motor neuron disease, and therefore, no direct comparison is possible between our study and previous work.[5,15,16] In a small-scale, randomised, double-blind crossover trial[18] of cramps in amyotrophic lateral sclerosis, THC was well tolerated but did not significantly alleviate cramp frequency or severity, or fasciculation intensity compared with placebo. Similarly, we did not note any significant changes in spasm intensity in our trial.

In patients with multiple sclerosis, the results of several trials have suggested that nabiximols and cannabinoids can efficaciously reduce spasticity, which is consistent with our results.[10,11] In most studies in multiple sclerosis, however, the primary outcome for efficacy was a 0–10 numeric rating scale, whereas in our study, improvement in the score on the spasticity numeric rating scale was not significant in the nabiximols group. Although the Ashworth Scale or its modified form has been used in previous positive studies of the efficacy of other antispastic treatments, it lacked sensitivity in studies of cannabinoid efficacy in multiple-sclerosis-related spasticity, and thus spasticity numeric rating scale scores or visual analogue scales have been used in subsequent multiple sclerosis studies.[9–14] The ideal objective measure of the highly complex symptom of spasticity does not exist. The Ashworth Scale, which has been used in previous studies in motor neuron disease and amyotrophic lateral sclerosis,[8,27,32] remains the most used and best validated objective measure of spasticity despite its well known limitations.[33] Furthermore, the Ashworth Scale might not represent patients' experience of spasticity, and self-reported measures might not faithfully represent the neurophysiological definition of spasticity. A disease-specific self-report scale has been developed in an attempt to overcome the limitations of available spasticity outcome measures in amyotrophic lateral sclerosis.[6]

Spasticity can be influenced by several factors and can change over time in motor neuron disease as a result of progressive lower or upper motor neuron involvement. Although to the best of our knowledge no systematic study has assessed the natural history of spasticity in patients with motor neuron disease, in a trial[8] assessing the role of physical activity in patients with amyotrophic lateral sclerosis, scores on the Ashworth Scale worsened over time in the control group,[8] which is consistent with our observations. Furthermore, theoretically disease progression involving lower motor neurons could mask the burden of upper motor neuron disease and thus paradoxically reduce spasticity.[8] However, we did not note any significant between-group differences in Medical Research Council sum scores.

Patient-reported outcomes have a growing role in clinical trials. In our trial, significantly more patients in the nabiximols group than in the placebo group had a global impression of improvement. Notably, during the open-label phase, the proportion of patients originally in the placebo group reporting an improvement rose to a level similar to that noted in the original nabiximols group; these results are consistent with those in previous reports in patients with multiple sclerosis.[13,28,29] Improvement in patients' global impressions of change might reflect the multiple symptomatic effects of cannabinoids that could be beneficial to patients with amyotrophic lateral scleroris.[11,20] Although the effects on spasms, sleep disruption, and spasticity numeric rating scale scores were not significant, the direction of change was consistently in favour of the active treatment, and the pain score improved significantly in the nabiximols group compared with the placebo group. However, this phase 2 randomised study was not sufficiently powered to show an effect on all secondary outcome measures. In further support of nabiximols efficacy is the general improvement in outcome measures recorded during the extension study in the original placebo group, even if the open-label design limits the value of these findings. Although pain is an often-neglected symptom in motor neuron disease, its prevalence has been reported to be as high as 51–80%, it negatively affects quality of life, and it necessitates specific treatment in 37–39% of patients.[34] Cannabinoids were efficacious in preclinical models of pain and are increasingly recognised as a valuable treatment option in cancer and neuropathic and non-neuropathic pain.[20,31] The causes of pain in patients with amyotrophic lateral sclerosis are not well understood, and musculoskeletal, cramps, contracture, spasticity, and neuropathic pain have all been implicated in the pathophysiology.[34] Therefore, the encouraging results of our exploratory trial suggest the need for further studies of the effects of nabiximols in different pain subtypes.

The main cannabinoid targets to deliver an antispastic effect are the CB1 receptors located on CNS synapses, targeting of which results in inhibition of presynaptic calcium influx and reduced release of glutamatergic neurotransmitters.[19,35] THC, a partial agonist at both CB1 and CB2 receptors, mimics the negative feedback action of the endocannabinoid anandamide, and thus reduces the excitatory effects of glutamate typical in spasticity.[35] Cannabidiol does not affect either CB1 or CB2 receptors at these pharmacological doses, but could inhibit the uptake—and weakly inhibit the breakdown—of anandamide.[19] The cannabinoid analgesic effects could be mediated by both CB1 and CB2 receptors.[20] CB1 receptors are expressed in nociceptive areas of the brain and periaqueductal grey matter, spinal cord, and peripheral nervous system. CB2 receptors are mainly concentrated in haemopoietic and immune cells, including microglia, and could have a role in pathogenesis of inflammatory pain.[20] Additionally, CBD could exert its analgesic and anti-inflammatory properties by antagonising tumour

necrosis factor α and enhancing adenosine receptor A2A signalling.[20]

Overall, nabiximols was well tolerated, and the adverse event profile in our trial was similar to that in previous reports, with nervous system disorders being the most frequent evens.[35,36] Although most adverse events were mild to moderate, during the randomised phase of the trial, adverse events were more common in the nabiximols group than in the placebo group. When participants in the placebo group switched to nabiximols during the open-label phase, the frequency of adverse events was similar to that in the nabiximols group during the double-blind phase. Conversely, the 50% reduction in the incidence of adverse events noted during the open-label phase in patients who were already receiving nabiximols suggests that a substantial number of adverse events could be related to the titration phase, consistent with previous reports in multiple sclerosis,[35,36] confirming the need for clinical monitoring in patients to whom cannabinoids are prescribed, particularly during first weeks of exposure and the titration phase. Individual side-effects should be carefully considered in the context of symptomatic treatment. The significant difference in the mean number of daily actuations between the nabiximols and placebo groups could be related to the perceived effect of treatment and, although highly variable between patients, could be indicative of the mean optimal dose balancing tolerability and efficacy. The mean number of daily actuations was similar between groups during the open-label phase. The tolerability of nabiximols is further shown by the fact that no patients withdrew from the randomised trial, whereas during the open-label study, only five (8%) of 59 patients withdrew for tolerability reasons, a similar proportion to that in previous reports.[12,36] In a meta-analysis[36] of the pivotal studies assessing the efficacy of cannabinoids in multiple-sclerosis-related spasticity, the estimated withdrawal or abandonment rate due to tolerability issues was 11·0% for treated patients, whereas in a large observational study[12] of experience with nabiximols in daily clinical practice, 268 (19%) of 1432 patients discontinued treatment because of adverse events. Furthermore, the fact that progressive involvement of lower motor neurons, increased disability, and development of dysphagia or respiratory failure could also contribute to drug discontinuation in patients with amyotrophic lateral sclerosis further supports the necessity of clinical monitoring to reassess and tailor pharmacological interventions.

Our study has several limitations. As detailed earlier in the discussion, there are general limitations in the measurement of spasticity. Furthermore, despite the double-blind design, the risk of bias associated with unmasking as a result of treatment side-effects cannot be excluded—especially given that no formal testing of the degree of blinding was done.[26] In view of the small sample size and short trial duration, we might not have discovered adverse events that occur with low frequency or that are related to medium-to-long-term cannabinoid exposure in motor neuron disease, which could be relevant to the potentially devastating disease course of amyotrophic lateral sclerosis. Conversely, the small sample size and short duration of the study provided little opportunity for the detection of a potential neuroprotective effect of cannabinoids in slowing disease progression, as has been suggested by the results of preclinical studies in rodent models of amyotrophic lateral sclerosis.[21–24]

This study is, to our knowledge, the first randomised controlled trial of safety and efficacy of a pharmacological treatment for spasticity and the first trial of nabiximols in motor neuron disease. Our results suggest that the study drug is well tolerated and provides first evidence of efficacy in terms of controlling spasticity in patients with motor neuron disease. Although nabiximols has been licensed in many countries for symptomatic control of spasticity in multiple sclerosis and cannabinoids are increasingly recognised as a valuable option for pain management, before we can confidently recommend the routine use of cannabinoids for symptomatic management of spasticity in patients with motor neuron disease, further studies are warranted to confirm our results.

Contributors

GC was the principal investigator and NR the project manager. NR, MC, and GC conceived and designed the study. OEF did the statistical analysis. NR, GM, GS, CL, YF, and RF provided clinical care, and recruited and followed up participants. All authors contributed to data interpretation. NR and GC wrote the first draft of the Article. LL, MC, and GC critically revised the Article for important intellectual content. All authors actively contributed to the writing and reviewing of the Article, and approved the final version.

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Declaration of interests

GM reports grants and non-financial support from the Italian Ministry of Health, and grants from Fondazione Italiana di Ricerca per la Sclerosi Laterale Amiotrofica and the EU Joint Programme—Neurodegenerative Disease Research Project. LL reports personal compensation or travel support from Abbvie, Biogen, Excemed, Merck Serono, Novartis, Teva, and Genzyme, and research support from Almirall, Biogen, Merck Serono, and Novartis. RF reports personal travel support fees from Kedrion, CSL Behring, and Baxter. GC reports personal fees from Almirall, Bayer, Biogen, Chugai, Excemed, Genzyme, Merck Serono, Novartis, Roche, Sanofi-Aventis, Serono Symposia International Foundation, Receptos, and Teva. All other authors declare no competing interests.

Data sharing

The CANALS study data, including all individual participant data that underlie the results reported in this Article, will be shared after deidentification, along with the study protocol, informed consent form, and analytic code. These data will be available from 4 months after Article publication until 5 years after Article publication. Requests and proposals

should be directed to the corresponding author, who will provide access to the CANALS study data to investigators and researchers who provide methodologically sound proposals for data use. To gain access, requesters will need to sign a data-access agreement.

Acknowledgments

This study was funded by Fondazione Italiana di Ricerca per la Sclerosi Laterale Amiotrofica (AriSLA) and Fondazione Vialli e Mauro (CANALS Project). GW Pharma provided the study drug and placebo.

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