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Meta-analysis of the efficacy and safety of Sativex (nabiximols), on spasticity in people with multiple sclerosis

Derick T Wade, Christine Collin, Colin Stott and Paul Duncombe

Abstract

Objective: To determine the efficacy of Sativex (USAN: nabiximols) in the alleviation of spasticity in people with multiple sclerosis.

Methods: The results from three randomized, placebo-controlled, double-blind parallel group studies were combined for analysis.

Patients: 666 patients with multiple sclerosis and spasticity.

Measures: A 0–100 mm Visual Analogue Scale (VAS, transformed to a 0–10 scale) or a 0–10 Numerical Rating Scale (0–10 NRS) was used to measure spasticity. Patients achieving a $\geq$30% improvement from baseline in their spasticity score were defined as 'responders'. Global impression of change (GIC) at the end of treatment was also recorded.

Results: The patient populations were similar. The adjusted mean change of the numerical rating scale from baseline in the treated group was −1.30 compared with −0.97 for placebo. Using a linear model, the treatment difference was −0.32 (95% CI −0.61, −0.04, $p = 0.026$). A statistically significant greater proportion of treated patients were responders (odds ratio (OR) = 1.62, 95% CI 1.15, 2.28; $p = 0.0073$) and treated patients also reported greater improvement: odds ratio 1.67 (95% CI 1.05, 2.65; $p = 0.030$). High numbers of subjects experienced at least one adverse event, but most were mild to moderate in severity and all drug-related serious adverse events resolved.

Conclusion: The meta-analysis demonstrates that nabiximols is well tolerated and reduces spasticity.

Keywords

multiple sclerosis, spasticity, cannabinoids, sativex, delta-9-tetrahydrocannabinol, cannabidiol, nabiximols

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Introduction

Systematic reviews of treatments used in the alleviation of spasticity, especially in people with multiple sclerosis (MS), have emphasized the weakness of the evidence for all currently used systemic drugs such as baclofen, tizanidine, dantrolene, diazepam, and gabapentin.[1,2] Recently, several studies have investigated the effectiveness of various cannabinoid-containing medications in patients with multiple sclerosis and spasticity.[3–10] Their individual results are consistent but weak. A meta-analysis of studies using the same preparation might reduce uncertainty about the effects of cannabinoids.

Meta-analysis of studies investigating drug treatment of spasticity is not easy. Different treatments are used and the recent trials of cannabinoid medicines have used preparations that vary both in their active ingredient(s), in their mode of presentation and in their route of administration. Second, different measures were used. This arises from the third difficulty, namely that there is no agreement on what spasticity is[11,12] and how it should be measured. Although the Ashworth scale[13] is the most widely used measure, there are concerns that it is unreliable and insensitive and that it only measures passive resistance to movement and not other aspects of spasticity.[12,14] Indeed a

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recent study has suggested that the Ashworth scale should 'never be used'![21]

Three randomized, controlled studies[4,6,7] have recruited similar patients and have used similar measures of efficacy and the same preparation, nabiximols (Sativex) which contains two principal cannabinoids – delta-9-tetrahydrocannbinol (THC) and cannabidiol (CBD) in a 1:1 ratio. All were placebo-controlled and performed in patients with MS who had insufficient benefit from their existing anti-spasticity medication. Nabiximols or placebo was administered as an add-on therapy, in addition to all existing medications.

Method

The meta-analysis used the original patient data collected in the three trials. The treatment used was nabiximols which is a THC:CBD endocannabinoid system modulator prepared under conditions of good manufacturing practice from extracts of selected chemical varieties (chemotypes) of cannabis plants (*Cannabis sativa* L.) with minor amounts of other cannabinoids and non-cannabinoid components (e.g. terpenes) in a solution containing ethanol, propylene glycol, and peppermint oil flavouring. It is presented as an oromucosal spray, with each 100 µl spray containing 2.7 mg of THC and 2.5 mg of CBD.

In two studies,[6,7] spasticity was the primary variable and all patients contributed data, whilst in the third study[4] spasticity was one of several primary symptoms assessed. In this third study[4] only the data from 140 of the 160 patients randomized who had spasticity as one of their primary symptoms were used.

Spasticity was assessed using a 100 mm Visual Analogue Scale (VAS) in one study[4] and a 0–10 Numerical Rating Scale (NRS) in the other two. Data from the 0–100 VAS were converted to a 0–10 scale using a simple linear transformation of dividing each recorded individual observation by 10. The endpoints used were 'no problem from spasticity' and 'the worst problem I can imagine'.

Resistance to stretch was measured using the Ashworth Scale[13] in one study[6] and the Modified Ashworth Scale (MAS)[14,16] in the other two.[4,7] In one study[4] eight muscle groups were scored using the MAS, in another 20 muscle groups were scored using the MAS,[7] and in the third,[6] only muscle groups with an AS score of ≥ 2 at baseline were scored throughout the study.

In all studies patients gave a rating of Global Impression of Change varying from much worse to much better (five points in one study[4] and seven in the other two); the analysis simply dichotomized the data into 'no change or worse' and 'better'.

In two of the studies,[6,7] patients were also asked to record spasticity using the Numerical Rating Scale on a daily basis.

The objective of the analysis was to pool and analyse the data to investigate the efficacy of nabiximols in comparison with placebo, and to consider data on safety and adverse effects. All presentations are based primarily on the intention-to-treat (ITT) population as reported in the individual study reports.

The statistical methods used were planned prior to unblinding of the third study, although the sensitivity analysis at week 6 was added subsequently.

The primary analysis has used data from the pre-planned final outcome assessment at 6 weeks in two studies[4,6] and at 14 weeks in the other study.[7] However data from week 6 in the last study have also been analysed.

The data were analysed using a general linear model in which the dependent variable was the change from baseline in spasticity assessment. Fixed factors included in the model were treatment group (nabiximols/placebo), study, and the treatment group by study interaction term. Baseline spasticity was included as a covariate. Homogeneity of variance was tested using Brown and Forsythe's test.[17] The interaction term was dropped from the model if not statistically significant ($p > 0.10$). The adjusted means for each treatment group are provided together with the estimated difference between treatments, 95% confidence intervals (CI) for the difference and corresponding *p*-value.

In order to assess the time course of effect over the first 6 weeks of treatment, summary statistics showing the change from baseline (and standard error) for each day (1–42) are shown graphically by treatment for two studies[6,7] combined; the other study[4] only had weekly assessments.

A 'responder' was defined as 'a patient who experiences a reduction in spasticity score of 30% or greater from baseline for the period of primary assessment'; this was derived from a study showing than an 18% change from baseline was the minimal clinically important difference.[18] The analysis was carried out using the Cochran–Mantel–Haenszel procedure adjusting for study. The odds ratio (OR) together with 95% CI is presented. Homogeneity of treatment effect was assessed using the Breslow–Day test and assessed for significance at the 10% level.

Due to the differences in Ashworth scales used and the numbers of muscle groups scored, it was unlikely that the raw effect size would be the same in the three studies and hence the analysis was carried out using summary statistics from the three studies and combining the standardized effect size. This analysis was carried out according to the methods outlined by Whitehead and Whitehead.[19] The pooled effect across studies was calculated together with 95% CI and the corresponding *p*-value.

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Table 1. Demographics

		Study 1 Wade et al. (2004)[4]		Study 2 Collin et al. (2007)[6]		Study 3 Collin et al. (2010)[7]	
Variable	Statistic	Nabiximols	Placebo	Nabiximols	Placebo	Nabiximols	Placebo
No. of patients	N	72	68	124	65	167	170
Gender	Female	41 (57%)	44 (65%)	80 (65%)	34 (52%)	106 (63%)	101 (59%)
Age (y)	N	72	68	124	65	167	170
	Mean	50.8	50.5	49.7	47.8	48.0	47.1
	SD	9.09	8.59	10.15	9.46	10.06	9.15
	Minimum	27	31	18	20	22	27
	Maximum	68	69	69	64	73	77
Spasticity at	N	71	67	122	64	166	169
baseline (0–10)	Mean	5.96	6.11	5.49	5.39	6.77	6.48
	SD	2.176	2.022	1.914	1.912	1.331	1.319
	Minimum	0.8	0.8	0.3	1.1	3.0	3.5
	Maximum	9.8	9.6	9.2	9.9	10.0	9.5
Ashworth Scale	N	68	64	120	64	163	165
at baseline[a]	Mean	1.25	1.26	2.41	2.44	1.54	1.45
	SD	0.939	1.111	0.454	0.403	0.785	0.722
	Minimum	0	0	2.0	2.0	0	0.2
	Maximum	3.5	4.8	3.9	3.8	4.4	3.9

[a]Modified Ashworth for Study 1 on scale (0–5) for eight muscle groups; Ashworth for Study 2 on scale (0–4) only muscle groups with a score of $\geq$2 at baseline assessed; Modified Ashworth for Study 3 on scale (0–5) for 20 muscle groups. Data presented are converted into score/muscle group.

Table 2. Pooled analysis of individual spasticity assessment using Visual Analogue Scale (VAS)/Numerical Rating Scale (NRS) data using a linear model

Treatment	*N*	Adjusted mean change from baseline	Treatment difference[a]	Standard error of difference	95% confidence interval for difference	*p*-value
Analysis at study endpoint[b]						
Nabiximols (N)	356	−1.30	−0.32	0.145	−0.61, −0.04	0.026
Placebo (P)	296	−0.97				
Analysis at week 6[c]						
Nabiximols (N)	356	−1.27	−0.31	0.140	−0.59, −0.04	0.026
Placebo (P)	296	−0.95				

[a]Treatment difference = nabiximols minus placebo.
[b]Intention-to-treat population; Timepoints: week 6 for Wade et al.[4] and Collin et al.[6] and weeks 13–14 for Collin et al.[7]
[c]Intention-to-treat population; Timepoints: week 6 for all three studies.

For all analyses, no imputation was done for subjects where any baseline or endpoint data were missing; these subjects were excluded from the analyses. Where subjects failed to complete the study period, then study endpoints were imputed using a last-observation-carried-forward approach.

Results

A total of 189 patients were randomized in the second study,[6] 337 patients in the third,[7] and 140 with spasticity as a symptom in the first.[4] In total, 363 patients were randomized to nabiximols and 303 patients to placebo. Participants in the three studies were similar in age and gender distribution and also spasticity severity at baseline, although patients in the third study had slightly greater baseline severity scores than patients in the other two studies. Demographics are summarized for the three studies by treatment group in Table 1.

The analysis of the outcome assessments of spasticity using individual patient data and a general linear model is summarized in Table 2. There was no indication of any statistically significant study-by-treatment interaction ($p > 0.10$) or heterogeneity of variance ($p > 0.10$).

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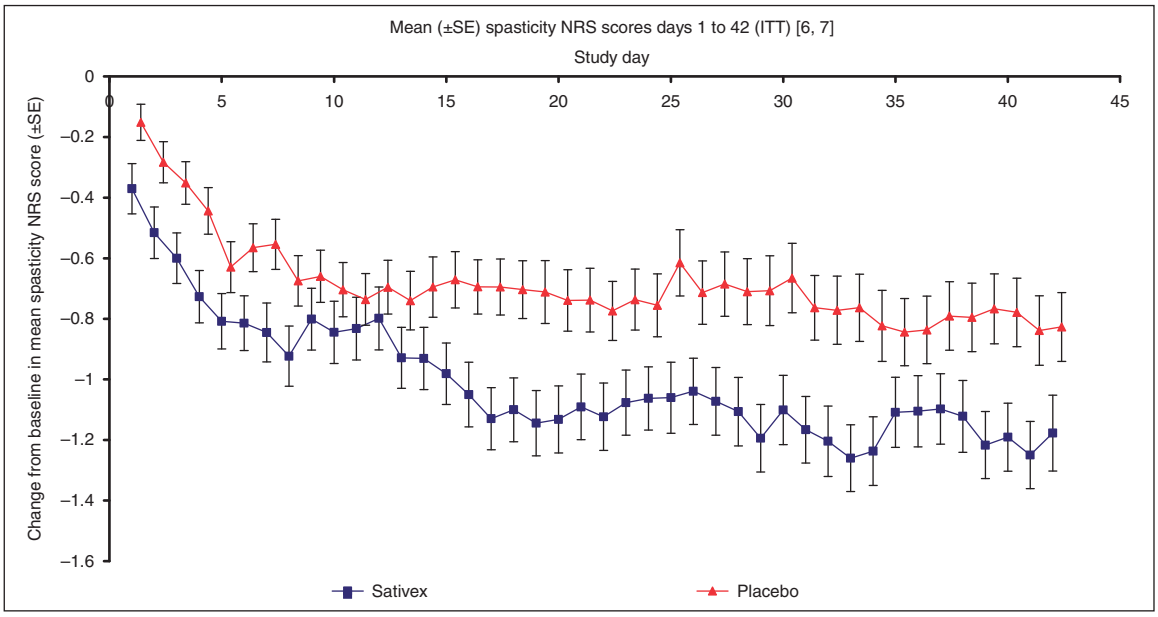

Figure 1. Change from baseline in spasticity over time.

Table 3. Responder analysis (30% or more reduction from baseline in spasticity assessment)

	N (%) with ≥30% reduction in spasticity				
Study	Nabiximols	Placebo	Odds ratio	95% confidence interval	*p*-value
Analysis at study endpoint[a]					
Study 1[4]	31/70 (44%)	21/63 (33%)	1.59	0.79, 3.22	
Study 2[6]	48/120 (40%)	14/64 (22%)	2.38	1.19, 4.78	
Study 3[7]	51/166 (31%)	42/169 (25%)	1.34	0.83, 2.17	
Pooled analysis	**130/356 (37%)**	**77/296 (26%)**	**1.62**[c]	**1.15, 2.28***	**0.0073**
Analysis at week 6[b]					
Study 1[4]	31/70 (44%)	21/63 (33%)	1.59	0.79, 3.22	
Study 2[6]	48/120 (40%)	14/64 (22%)	2.38	1.19, 4.78	
Study 3[7]	44/166 (27%)	38/169 (22%)	1.24	0.76, 2.05	
Pooled analysis	**123/356 (35%)**	**73/296 (25%)**	**1.57#**	**1.11, 2.23***	**0.014**

[a]Intention-to-treat population; Timepoints: week 6 for Study 1 and Study 2 and weeks 13–14 for Study 3.
[b]Intention-to-treat population; Timepoints: week 6 for all three studies.
[c]Adjusted for study.

However, the primary analysis based on the individual study endpoint and the ITT population showed a statistically significant difference in favour of nabiximols compared with placebo (difference −0.32, 95% CI −0.6, −0.04; $p = 0.026$). Analyses using the week-6 endpoint for all studies rather than the individual study endpoints gave very similar results. Meta-analyses using the summary statistics from each study gave the same results (data not shown).

Figure 1 uses the summarized daily scores from 526 patients ($n = 291$ nabiximols, $n = 235$ placebo) over the first 42 days from the two studies with daily recording[6,7] to show the change from baseline in spasticity score. Both groups improved during the first week; the change in the placebo group remained relatively constant from around day 10 until day 42 whilst the nabiximols group continued to show improvement up to day 16 and the improvement is maintained thereafter. The maximum difference between nabiximols and placebo is achieved after approximately 2 weeks treatment.

At the end of study time-point, 130 (37%) of 356 patients with post-randomization efficacy data available were responders on nabiximols and a pooled analysis using the Cochran–Mantel–Haenszel procedure in SAS (version 9.1, SAS Institute Inc, USA) adjusting for the study endpoint showed this proportion to be significantly greater than the 77 responders out of 296 patients (25%) on placebo ($p = 0.0073$; Table 3).

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Table 4. Global Impression of Change (GIC) Improved versus Not Improved

Study	N (%) with any improvement (intention-to-treat population)		Odds ratio	95% confidence interval	*p*-value
	Nabiximols	Placebo			
Study 1[4]	31/72 (43%)	18/68 (26%)	2.10	1.03, 4.28	
Study 2[6]	66/116 (57%)	31/64 (48%)	1.41	0.76, 2.59	
Study 3[7]	72/141 (51%)	56/144 (39%)	1.64	1.02, 2.62	
Pooled analysis	**169/329 (51%)**	**105/276 (38%)**	**1.66**[a]	**1.19, 2.30**[a]	**0.0036**

[a]Adjusted for study.

The point estimate of the odds ratio (OR) was 1.62 (95% CI 1.15, 2.28) indicating that the probability of getting a response of 30% or more improvement in spasticity score was 62% greater with nabiximols than placebo.

At the 6-week time-point, the proportion of responders on nabiximols (123 of 356) was also significantly greater than the proportion of responders on placebo ($p = 0.014$). The estimate of the odds ratio based on the week-6 endpoint was very similar (OR = 1.5, CI 1.11, 2.23) to that of the end of study time-point. The analysis did not indicate any heterogeneity of treatment effect across the three studies for the analysis based on either time endpoint ($p > 0.10$).

The analysis of Global Impression of Change was carried out using the Cochran–Mantel–Haenszel procedure in SAS adjusting for study. The results are summarized in Table 4. The analysis did not indicate any heterogeneity of treatment effect across studies ($p > 0.10$). The odds ratio of seeing an improvement in Global Impression of Change on nabiximols compared with placebo was 1.66 (95% CI 1.19, 2.30) and was statistically significant ($p = 0.0036$).

In the analysis of the Ashworth Scale score results, the meta-analysis was based on the standardized effect size in the three studies due to the different scoring systems used. There was no statistically significant difference between treatments ($p = 0.75$). It is of note that seven of 140 subjects from one study[4] and a single subject (of 337) from another study[7] were assessed at baseline as having a zero Ashworth Score. All subjects had been clinically diagnosed as suffering from spasticity and all provided a self assessment of spasticity and/or spasms which identified them as suffering from spasticity. In neither study was a positive Ashworth score a criterion for inclusion.

The incidence of treatment emergent, treatment-related adverse events are presented in Table 5. Two hundred and eighty-eight (79.3%) patients treated with nabiximols experienced at least one event, compared with 169 (55.8%) placebo patients. Most adverse events (AEs) were mild or moderate in severity in both treatment groups (84.6% versus 93.4%). There were 21/363 (5.8%) subjects in the nabiximols group with serious adverse events (SAEs), compared with 13/303 (4.3%) in the placebo group. All treatment-related SAEs resolved.

The following system organ classes had greater than a 3% difference in incidence of AEs between nabiximols and placebo: nervous system disorders (54.5% versus 26.4%); gastrointestinal disorders (29.6% versus 19.4%); general disorders and administration site reactions (29.2% versus 19.1%) psychiatric disorders (18.5% versus 5.6%); ear and labyrinth disorders (nabiximols versus placebo: 7.4% versus 2.3%); and musculoskeletal and connective tissue disorders (5.5% versus 2.0%). Overall, the single most common adverse reaction in the nabiximols group was dizziness, in 32% of patients, compared with 11% of placebo patients.

There were few treatment-emergent AEs which led to cessation of therapy (Table 6). Forty patients (11.0%) withdrew from treatment on nabiximols. The most frequent events leading to withdrawal were nausea in 10 subjects, dizziness in nine subjects, and vertigo in three subjects. No other AE accounted for more than two withdrawals. This compares with 11 patients (3.6%) who withdrew from treatment with placebo. The most common AEs leading to withdrawal in the placebo group were urinary tract infection (in three patients) dizziness and vomiting (in two subjects each).

Discussion

This meta-analysis of individual patient data from 666 patients with multiple sclerosis who had spasticity not adequately controlled using existing treatments and were then given nabiximols (363) or placebo (303) shows that there is a definite reduction in patient-reported problems; that the effects of nabiximols are usually evident within 3 weeks; and that about one-third of people given nabiximols as an add-on will gain at least a 30% improvement from baseline. The treatment appears reasonably safe. The three studies providing these data[4,6,7] were randomized, double-blind, placebo-controlled, parallel-group studies (two studies of 6-week treatment duration and the other of

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Table 5. Adverse events: treatment emergent, treatment-related adverse events

	Nabiximols ($n = 363$)		Placebo ($n = 303$)	
System organ class	*N*	%	*N*	%
Subjects with an event	**288**	**79.3**	**169**	**55.8**
Cardiac disorders	5	1.4	2	0.7
Ear and labyrinth disorders	27	7.4	7	2.3
Eye disorders	14	3.9	4	1.3
Gastrointestinal disorders	110	29.6	61	19.4
General disorders and administration site conditions	106	29.2	58	19.1
Hepatobiliary disorders	1	0.3	0	0
Infections and infestations	8	2.2	5	1.7
Injury, poisoning, and procedural complications	5	1.4	6	2.0
Investigations	10	2.8	2	0.7
Metabolism and nutrition disorders	11	3.0	1	0.3
Musculoskeletal and connective tissue disorders	20	5.5	6	2.0
Nervous system disorders	198	54.5	80	26.4
Psychiatric disorders	67	18.5	17	5.6
Renal and urinary disorders	8	2.2	1	0.3
Reproductive system and breast disorders	1	0.3	1	0.3
Respiratory, thoracic, and mediastinal disorders	11	3.0	8	2.6
Skin and subcutaneous tissue disorders	5	1.4	2	0.7
Vascular disorders	6	1.7	3	1.0

Table 6. Adverse events: treatment emergent, adverse events leading to withdrawal

	Nabiximols ($n = 363$)		Placebo ($n = 303$)	
System organ class	*N*	%	*N*	%
Subjects with an event	**40**	**11.0**	**11**	**3.6**
Ear and labyrinth disorders	3	0.8	0	0
Eye disorders	1	0.3	0	0
Gastrointestinal disorders	20	5.5	3	1.0
General disorders and administration site conditions	5	1.4	2	0.7
Infections and infestations	4	1.1	4	1.3
Neoplasms (benign, malignant, and unspecified)	2	0.6	0	0
Nervous system disorders	19	5.2	4	1.3
Psychiatric disorders	7	1.9	0	0
Renal and urinary disorders	3	0.8	0	0
Respiratory, thoracic, and mediastinal disorders	1	0.3	1	0.3
Vascular disorders	1	0.3	0	0

14-week treatment duration). This dataset is similar in size to that of the CAMS study dataset ($n = 657$).[8]

The subjects enrolled in these studies were those who were not adequately controlled by existing anti-spasticity medication (i.e. were treatment-resistant), and who had significant residual spasticity. It is of note that eight subjects overall entered the study despite having a baseline Ashworth Score of zero. In seven of the eight subjects the Ashworth Score was assessed as being at least 1 later in the study. On the one hand, it could be questioned whether these patients did indeed have spasticity; on the other hand, a positive Ashworth Score was not an entry criterion and it may be that patients with spasticity may, on occasion, be assessed as having an Ashworth score of zero. The consensus in the literature that a single Ashworth

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scale score is inadequate to assess the severity or the degree of functional impairment of spasticity has recently been summarized by Fleuren et al.[15]

This meta-analysis should be put in the context of other studies of treatments for spasticity. The evidence supporting botulinum toxin as a treatment for focal spasticity is strong, particularly in the arm; the evidence supporting other anti-spastic drugs and physical methods is weak. The numbers of patients involved in most past studies have been small, the measures used have not included detailed assessment of patient experience and the standard of the designs low (most studies were carried out many years ago).

There are no other meta-analyses of anti-spastic drug treatments. This meta-analysis was possible because similar methods and measures were used and all the data were held by one organization. This meta-analysis is unusual in that it can report upon additional features. First the speed of response to medication can be given; most people who will benefit do so within 4 weeks. No other studies have such detailed information. Second the effects and safety over a longer period than that included in most studies can be reported; the side-effects are common but rarely sufficient to stop treatment. Third, it can estimate the number of patients who have intractable spasticity who nonetheless might respond, about one-third. Of course this one third may include some placebo responders but in clinical practice this applies to all drugs prescribed and is no different in this case.

The 0–10 Numeric Rating Scale is recommended as a preferred outcome measure in the assessment of interventions in chronic pain,[20] but has not been widely used in studies of anti-spasticity medications. It has the benefit of allowing the patient to express their own daily experience of spasticity and has recently been validated.[17,21] The homogeneity of the Numeric Rating Scale data seen in this meta-analysis adds to the evidence that it is a suitable assessment tool and possibly an alternative to the Ashworth Scale which several research groups have criticized.[15,22]

The potential weaknesses and limitations of this study are as follows. The studies were sponsored by the manufacturer who also has the data. However analysis was undertaken by an independent company and the company have not controlled the analysis or writing. The reader will have to judge how much influence there has been. Second, though the studies were similar in most aspects, there were slight differences in measurement techniques and times. However the degree of similarity is far greater than in most meta-analyses undertaken and the supplementary analyses suggest that the differences were not material. With any medicine that has central nervous system effects, there is a possibility that patients may become unblinded to treatment allocation. There is no evidence that this has occurred with nabiximols to an extent that affects the outcome of these studies.[23] This meta-analysis has not investigated the long-term effects of nabiximols but a long-term, open-label study has suggested that the effect persists with needing any increase in dose.[5]

The results would suggest that nabiximols has a role in the management of spasticity that is not adequately controlled using other available treatments, and that a 4-week trial would be justified. Other studies have shown that it can be stopped suddenly without risk[5] so if there is no benefit at 4 weeks, it could simply be stopped. The dose needed seems to remain stable once established.[5] Finally the side-effects expected seem similar to those of most existing medications for the same problem.

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