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CASE SERIES

Effect of nabiximols oromucosal spray (Sativex®) on symptoms associated with multiple sclerosis-related spasticity: a case series

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Abstract

Spasticity and its related symptoms of spasms, pain, sleep disturbance and bladder dysfunction are common in persons with multiple sclerosis (MS) and may be interconnected through a common pathophysiology and/or may trigger and worsen each other. Tetrahydrocannabinol–cannabidiol (nabiximols) oromucosal spray (Sativex) is an add-on treatment for adults with moderate-to-severe MS spasticity who fail to respond adequately to conventional oral medications. There is evidence that nabiximols can ameliorate spasticity-associated symptoms irrespective of its effect on spasticity. This case series describes 12 adults with MS spasticity who were evaluated for symptom evolution before and during adjunctive nabiximols treatment. Nabiximols reduced spasticity severity in 11 patients, of whom 8 had a clinically important ≥30% improvement in 0–10 Numeric Rating Scale scores during treatment. In 7 patients who reported spasms, severity was reduced or spasms were absent/unnoticeable during nabiximols treatment. Walking distance was improved in 8 patients. Pain severity was reduced in 11 patients, and sleep disorder was completely resolved in 3 patients and improved in 8. Bladder dysfunction was improved in 6 of 7 patients with baseline symptoms. Two patients arguably should have discontinued nabiximols sooner: one had a limited response and experienced adverse effects throughout 6 months of treatment; the other was a non-responder who suffered a fall due to dizziness after 7 weeks of use. Overall, this case series shows, at an individual patient level, that the benefits of nabiximols extend beyond spasticity to include spasticity-related symptoms.

Keywords: adjunctive therapy, case series, multiple sclerosis spasticity, nabiximols oromucosal spray, Sativex.

Citation

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Introduction

Multiple sclerosis (MS) is a chronic inflammatory, demyelinating and neurodegenerative disease of the central nervous system.[1] Persons with MS can develop symptoms in any number of domains across mobility, spasticity, pain, hand function, vision, fatigue, cognition, bowel/bladder function, sensory function, depression and tremor/coordination, with considerable inter-individual variation in the patterns of impairment.[2] Spasticity occurs in at least two-thirds of patients with MS[2,3] and is frequently associated with spasms, pain, fatigue, sleep disturbance and bladder dysfunction.[4] Pharmacological management of MS symptoms typically targets individual symptoms, often leading to polypharmacy, which increases the risk of adverse effects, drug–drug interactions and exacerbation of disease-related symptoms.[5,6]

Tetrahydrocannabinol–cannabidiol (nabiximols) oromucosal spray (Sativex®, GW Pharmaceuticals, Cambridge, UK) is an add-on treatment for adult patients with moderate-to-severe MS spasticity who fail to respond adequately to conventional oral antispasticity medication.[7] Although the exact mechanisms of cannabinoid-based medicines are complex and not fully understood, cannabinoid receptors are distributed widely throughout the body, including in the central and peripheral nervous systems and peripheral organs,[8] suggesting potential as a therapeutic target for various diseases.[9] In experimental and observational studies of nabiximols in patients with MS spasticity, improvements

were reported not only in spasticity but also in sleep quality, pain and bladder symptoms.[10–13] This observation, coupled with clinical experience that these symptoms tend to cluster, led to the concept of the 'spasticity-plus syndrome', which suggests that the symptoms may be interconnected through a common pathophysiology or, at minimum, may trigger or worsen each other.[14,15]

Retrospective analyses of data captured from a large cohort of patients with moderate-to-severe MS spasticity treated in routine practice showed that nabiximols ameliorated spasticity-related symptoms (e.g. spasms/cramps, pain, bladder disorders and sleep disturbances) in a relevant proportion of the population,[16,17] including in non-responders, based on the current accepted therapeutic response threshold of ≥20% improvement from baseline in spasticity severity after 4 weeks of treatment.[7] To gain a detailed understanding of the effect of add-on nabiximols on spasticity-related symptoms at an individual level, this case series evaluates symptom evolution in patients with MS spasticity and variable baseline spasticity-related symptoms. The evaluation encompassed a wide range of clinician-reported and patient-reported outcomes.

Methods

The case series describes symptom evolution in 12 adults aged ≥18 years with moderate-to-severe MS spasticity who began treatment with nabiximols oromucosal spray due to inadequate relief using other antispasticity medications. Cases were selected by the authors as being illustrative of the spectrum of patients with MS spasticity encountered in routine clinical practice.

Patients were receiving ongoing neurological treatment and were examined and questioned at the time that the case reports were prepared. A pro forma case report form (Supplementary file; available at: https://www.drugsincontext.com/wp-content/uploads/2024/01/dic.2023-10-1-Suppl.pdf) was used to capture patients' demographic characteristics, disease history (MS, MS-related spasticity, concomitant diseases), and clinical status and quality of life (QoL) before and during nabiximols treatment. Clinical details prior to initiation of nabiximols treatment were collected mainly retrospectively by chart review or, as necessary, by asking the patient to think back and assign a rating retrospectively.

Patient clinical status was evaluated using the clinician-rated Ashworth scale; clinician-rated Expanded Disability Status Scale (EDSS); patient-rated spasticity 0–10 Numeric Rating Scale (NRS); patient-reported spasms frequency (number of spasms/day; presence of daytime/nighttime spasms) and spasms severity (mild, moderate, severe); clinician-rated degree of mobility impairment (mild, moderate, severe) due to MS-related spasticity and mobility parameters (gait, walking distance); and patient-rated 0–10 NRS for each of pain, bladder dysfunction and sleep disorder. For context, a ≥20% and ≥30% reduction from baseline in a symptom severity score on the 0-10 NRS represents a minimal clinically important difference and a clinically important difference, respectively.[18] Data were also collected about medications used to treat MS spasticity and MS spasticity-associated symptoms before and after add-on nabiximols as well as details of nabiximols treatment. Details regarding nabiximols tolerability (as documented in patient medical charts or by direct questioning) and the treating physician's clinical assessment of the main changes associated with nabiximols use were recorded using free-text fields. Health-related QoL was assessed informally by asking patients to comment on any perceived changes in their QoL or ability to perform daily activities since starting treatment with nabiximols.

All patient data have been deidentified to ensure confidentiality.

Results are reported descriptively. No statistical analyses were conducted.

Statement of ethics

Ethical approval was not required for this case series in accordance with local or national guidelines.

Results

The 12 patients (9 women, 3 men) were aged from 26 to 75 years. MS type was secondary progressive MS (*n*=7), relapsing-remitting MS (*n*=4) or primary progressive MS (*n*=1). Time from diagnosis of MS ranged from 5 to 39 years. EDSS scores (4 to 7.5/8.0) before nabiximols treatment indicated moderate-to-severe disability (Table 1).

The duration of MS-related spasticity ranged from 3 to 32 years. Previous treatments for MS spasticity included single-agent baclofen, tizanidine, tolperisone or dantrolene, combination therapy with baclofen plus tizanidine and/or tolperisone, intrathecal triamcinolone acetonide, botulinum toxin, and physiotherapy. Prior to treatment with nabiximols, spasticity severity as evaluated on the spasticity 0–10 NRS was mild (*n*=1), moderate (*n*=2) or severe (*n*=9) (Table 1).

MS spasticity-associated symptoms evaluated were spasms, pain, bladder dysfunction, mobility impairment and sleep disturbances (Table 1). Prior to beginning nabiximols treatment, 7 patients were experiencing spasms of self-assessed moderate (*n*=3) or severe (*n*=4)

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Table 1. Demographics and clinical characteristics before treatment with add-on nabiximols.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11	Case 12
Sex	Female	Female	Male	Female	Female	Female	Female	Male	Female	Male	Female	Female
Age (years)	75	57	48	52	59	48	40	60	32	63	26	48
Time from MS diagnosis (years)	39	13	17	6	38	35	13	17	5	36	5	10
MS type	SPMS	RRMS	RRMS	SPMS	SPMS	PPMS	SPMS	SPMS	RRMS	SPMS	RRMS	SPMS
EDSS score	6	4	5	6.5	6	7	6.5–7.0	7.5–8.0	4	7–8	7–8	5–6
MS-related spasticity												
Duration of MS-related spasticity (years)	22	7	12	3	32	21	10–11	15	3	28	3	6
Previous treatments for MS spasticity	Baclofen up to 50 mg; intrathecal triamcinolone acetonide 80 mg; botulinum toxin	Baclofen 20 mg; tizanidine 2 mg; physiotherapy	Baclofen 20 mg	Baclofen 15 mg; physiotherapy	Tizanidine (up to 16 mg); baclofen (up to 80 mg); baclofen + tizanidine (from 2005); triamcinolone acetonide intrathecally (several times a year from 2010)	Tizanidine (up to 8 mg/day); baclofen (up to 60 mg); tolperisone (up to 200 mg/day); baclofen + tolperisone + tizanidine (from 2005)	Tizanidine (up to 20 mg/day); baclofen (up to 80 mg/day); baclofen + tizanidine (from 2017); triamcinolone acetonide intrathecally (several times a year from 2017–present)	Dantrolene (up to 200 mg/day until 2009); tolperisone (off-label up to 600 mg/day); tizanidine (up to 20 mg/day); baclofen (up to 120 mg/day); tizanidine + tolperisone + baclofen (from 2012); triamcinolone acetonide intrathecally (several times a year from 2017–2022)	Baclofen (up to 80 mg) + tizanidine (up to 12 mg)	Tolperisone 350 mg; baclofen 100 mg; tizanidine 16 mg; triamcinolone acetonide (repeated 80 mg)	Baclofen 85 mg; tizanidine 20 mg	Baclofen 80 mg; tizanidine 24 mg; triamcinolone acetonide (up to 80 mg); gabapentin 1800 mg
Spasticity severity	Severe	Moderate	Mild	Moderate	Severe	Severe legs/ mild hands	Severe	Severe	Severe	Severe	Severe	Severe
Spasticity 0–10 NRS	8	4	3	7	8–10	8–10 legs & 2–4 hands	8–10	9–10	9	8–10	8–10	8–10

(*Continued*)

Table 1. (Continued)

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11	Case 12
Spasticity-associated symptoms: spasms												
Spasms severity	Severe	None	Moderate	None	Moderate	None	Moderate	None	Severe	Severe	None	Severe
Spasticity-associated symptoms: pain												
Pain severity	Severe	Moderate	Moderate	Moderate	Moderate/ severe	Moderate/ severe	Moderate/ severe	Moderate/ severe	Severe	Severe	Moderate/ severe	Severe
Pain 0–10 NRS	8	5	4	5	5–8	7–10	5–8	5–10	8	8–10	6–8	8–10
Spasticity-associated symptoms: bladder dysfunction												
Bladder dysfunction severity	Moderate	None	Moderate	None	Moderate/ severe	None	Moderate/ severe	Severe	Moderate	None	None	Severe
Bladder dysfunction 0–10 NRS score	5	-	4	-	5–8	-	5–8	8–10	5	-	-	8
Spasticity-associated symptoms: mobility impairment												
Mobility impairment	Severe	Moderate	Mild	Severe	Severe	Severe	Severe	Severe	Severe	Severe	Severe	Severe
Walking distance	5 m with a rollator, otherwise wheelchair	About 500 m	500 m	Approx 500 m with a rollator	2–8 m	2–5 m	5–25 m	Few steps	Approx 500 m	Few steps	5–10 m with help/ equipment	Few steps
Spasticity-associated symptoms: sleep disturbances												
Sleep disorder severity	Severe	Moderate	Moderate	Moderate	Severe	Moderate	Severe	Severe	Severe	Severe	None	Severe
Sleep disorder 0–10 NRS score	8	4	4	5	8–10	5–6	8–10	8–10	8	8	–	8–10

EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; NRS, Numeric Rating Scale; PPMS, primary progressive MS; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS.

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Table 2. Change in MS-related spasticity and MS spasticity-associated symptoms after treatment with add-on nabiximols.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11	Case 12
Treatment with nabiximols												
Duration of nabiximols therapy	6 years	10 months	48 months	6 months	4 years	9 years	3 years	8 months	10 months	61 months	2 months	20 months
Nabiximols dose (sprays/day)	10	4	4	5	4–7	2–7	4–8	8–12	7	11	12	7
Concomitant therapy: dose reduction	Baclofen (12.5 mg)	Tramadol	NR	NR	Triamcinolone acetate; tizanidine	Tolperisone; baclofen; tizanidine	Tizanidine	Tizanidine, tolperisone + baclofen combination temporarily replaced by lower doses of baclofen + tizanidine	Baclofen; tizanidine	Baclofen	None	Tizanidine; gabapentin
Concomitant therapy: discontinued	Intrathecal triamcinolone acetonide	NR	Baclofen	NR	Baclofen	Tolperisone	Baclofen; triamcinolone acetate (from October 2021); gabapentin; trimipramine	Tolperisone	Tizanidine (at night)	Off-label tolperisone; tizanidine	None	Metamizole; tramadol; tizanidine
Disability status												
Change in EDSS score	No change (6)	↓ 4 to 3	↓ 5 to 4	↓ 6.5 to 6.0	↓ 6.0 to 5.0–5.5	↓ 7.0 to 5.5	↓ 6.5–7.0 to 6.5	No change (7.5–8.0)	No change (4)	↓ 7–8 to 6–7	No change (7–8)	No change (5–6)
MS spasticity												
Change in spasticity severity	No change (severe)	Moderate to mild	No change (mild)	No change (moderate)	Severe to mild/moderate	Severe/mild to mild	Severe to mild/moderate	Severe to moderate	Severe to mild	Severe to moderate	No change (severe)	No change (severe)
Change in spasticity 0–10 NRS	↓ 8 to 7	↓ 4 to 2	↓ 3 to 1	↓ 7 to 4	↓ 8–10 to 4–6	↓ 8–10 (legs) & 2–4 (hands) to 2–5	↓ 8–10 to 4–6	↓ 9–10 to 7–8	↓ 9 to 4	8–10 to 5–7	No change: 8–10 to 8–10	No change: 8–10 to 7–10
Spasticity-associated symptoms: spasms												
Change in spasm severity	↓ Severe to mild	None at baseline	↓ Moderate to absent	None at baseline	↓ Moderate to mild	None at baseline	↓ Moderate to absent	None at baseline	↓ Severe to mild	↓ Severe to mild/moderate	None at baseline	↓ Severe to moderate

(*Continued*)

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Table 2. (Continued)

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11	Case 12
Spasticity-associated symptoms: pain												
Change in pain severity	↓ Severe to mild	↓ Moderate to mild	↓ Moderate to mild	↓ Moderate to mild	↓ Moderate/ severe to mild	↓ Moderate/ severe to mild	↓ Moderate/ severe to mild	↓ Moderate/ severe to mild/ moderate	↓ Severe to mild	↓ Moderate to mild	No change (moderate/ severe)	↓ Severe to mild
Change in pain 0–10 NRS	↓ 8 to 2	↓ 5 to 3	↓ 4 to 1	↓ 5 to 3	↓ 5–8 to 2–4	↓ 7–10 to 2–3	↓ 5–8 to 0–2	↓ 5–10 to 4–7	↓ 8 to 3–4	↓ 8–10 to 3–5	No change (6–8)	↓ 8–10 to 2
Spasticity-associated symptoms: bladder dysfunction												
Change in bladder dysfunction severity	No change (moderate)	None at baseline	↓ Moderate to mild	None at baseline	↓ Moderate/ severe to mild	None at baseline	↓ Moderate/ severe to mild	↓ Severe to mild	↓ Moderate to mild	None at baseline	None at baseline	↓ Severe to absent
Change in bladder dysfunction 0–10 NRS score	↓ 5 to 3	-	↓ 4 to 1	-	↓ 5–8 to 2–3	-	↓ 5–8 to 2–3	No change (8–10)	↓ 5 to 3	-	-	↓ 8 to 0
Spasticity-associated symptoms: mobility impairment												
Change in mobility impairment severity	No change (severe)	↓ Moderate to mild	No change (mild)	↓ Severe to moderate	↓ Severe to moderate	↓ Severe to moderate	↓ Severe to moderate	No change (severe)	↓ Severe to moderate	↓ Severe to moderate/ severe	No change (severe)	No change (severe)
Change in walking distance	No change (5 m with rollator)	↑ ~500 m to 1000 m (maximum)	↑ 500 m to >500 m	↑ ~200 m with a rollator to ~500 m with a rollator	↑ 2–8 m to 10–25 m	↑ 2–5 m to 15–35 m	↑ 5–25 m to ≥25 m with rollator	No change (few steps)	↑ ~500 m to >800 m	↑ Few steps to rollator-aided 10–25 m	No change (5–10 m)	No change (few steps)
Spasticity-associated symptoms: sleep disturbances												
Change in sleep disorder severity	↓ Severe to mild	↓ Moderate to mild	↓ Moderate to mild	↓ Moderate to mild	↓ Severe to none	↓ Moderate to none	↓ Severe to none	↓ Severe to moderate/ severe	↓ Severe to mild	↓ Severe to mild	None at baseline	↓ Severe to mild
Change in sleep disorder 0–10 NRS score	↓ 8 to 2	↓ 4 to 3	↓ 4 to 1	↓ 5 to 3	↓ 8–10 to 0	↓ 5–6 to 0	↓ 8–10 to 0	↓ 8–10 to 7–9	↓ 8 to 2	↓ 8 to 2	–	↓ 8–10 to 1

(*Continued*)

Table 2. (Continued)

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11	Case 12
Quality of life / Activities of daily living												
Quality of life/ activities of daily living	Subjective marked improvement	"Good"	Subjective improvement	NR	Subjective significant improvement	Subjective significant improvement	Subjective significant improvement	Subjective non-improvement; worsened by adverse effects	Subjective improvement in sleep and walking; general condition improved due to less medication	Improved: fewer spasms, better sleep, standing better, rollator-aided walking improved and transfer to wheelchair possible	Non-responder	NR

EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; NR: not reported; NRS, Numeric Rating Scale.

intensity. Pain was present in all 12 patients and was moderate (*n*=3), moderate/severe (*n*=5) or severe (*n*=4) as per the 0–10 NRS score. Seven patients had bladder dysfunction, which was moderate (*n*=3), moderate/severe (*n*=2) or severe (*n*=2) according to the 0–10 NRS score. Overall mobility impairment due to MS-related spasticity was rated by clinicians as mild (*n*=1), moderate (*n*=1) or severe (*n*=10). Walking distance ranged from a few steps to approximately 500 m. Eleven patients had spasticity-associated sleep disorder, which was moderate (*n*=4) or severe (*n*=7) as per the 0–10 NRS score.

Outcomes following add-on nabiximols therapy

Details of nabiximols treatment, changes in concomitant antispasticity therapy, and changes in MS spasticity and associated symptoms during treatment with add-on nabiximols in this series of patients are summarized in Table 2.

The duration of nabiximols treatment ranged from 2 months to 9 years, and the nabiximols dose ranged from 2 to 12 sprays/day, averaging about 7 sprays/day. In nine patients, the dose of concomitant antispasticity medication, mainly single-agent tizanidine (*n*=5) and baclofen (*n*=4), was reduced after starting nabiximols treatment. In nine patients, one or more concomitant antispasticity medications, mainly baclofen (*n*=3), tizanidine (*n*=3) and tolperisone (*n*=3), were discontinued.

Eight patients (Cases 2, 3, 4, 5, 6, 7, 9 and 10) had a ≥30% reduction in their spasticity 0-10 NRS score during treatment with nabiximols. In three patients, the change in the spasticity 0-10 NRS score with nabiximols did (Case 8) or did not (Cases 1 and 12) achieve the minimal clinically important difference of a ≥20% reduction from baseline. One patient (Case 11) was a nabiximols non-responder.

EDSS scores were improved (by 0.5–1.5 points) during nabiximols treatment in 7 patients and were unchanged in 5 patients.

In all 7 patients who were experiencing spasms prior to starting nabiximols, spasms severity decreased or the spasms abated during treatment. Pain 0–10 NRS scores decreased in 11 patients during nabiximols treatment. Amongst 7 patients with bladder symptoms before nabiximols treatment, bladder dysfunction 0–10 NRS scores decreased in 6 patients and were unchanged in 1 patient. Walking distance was improved in eight patients, most of whom (*n*=5) had an improvement in overall mobility impairment from severe before nabiximols treatment to moderate during treatment. Sleep disturbances were reported in 11 patients before nabiximols started and, during treatment, were resolved in 3 patients and reduced in 8 patients.

According to the patients' subjective perceptions of their QoL during nabiximols treatment, QoL was described as 'good' by 1 patient (Case 2) and was improved in 8 cases. In 1 patient (Case 8), QoL worsened during treatment due to the presence of persistent adverse effects (dizziness, apathy and nightmares).

Initial dizziness at the start of nabiximols treatment in 1 patient (Case 4) resolved with continued treatment. A nabiximols non-responder (Case 11) had a fall due to dizziness after 7 weeks of use, which was deemed treatment related; nabiximols was discontinued at 8 weeks.

A descriptive summary of the effect of add-on nabiximols on MS-related spasticity and associated symptoms in the individual cases is provided below. As efforts were taken to limit the size of the tables, the narratives may contain details not displayed in the tables.

Case 1

Following a diagnosis of MS in 1993, the patient suffered many relapses, including multiple spinal relapses. During the past 20 or more years, she had experienced a progressive deterioration in walking ability, mainly due to high-grade spastic paraparesis. Spasticity and associated symptoms, particularly painful nocturnal spasms, caused significant impairment of sleep and overall QoL. Oral baclofen (up to 50 mg) was not sufficiently effective and caused considerable fatigue, although treatment was maintained at a low dose. Repeated intrathecal triamcinolone injections led to a moderate improvement in spasticity. In 2016, the patient began treatment with nabiximols, which improved the spasms and associated pain. During nabiximols treatment, significant improvements in pain and sleeping (Table 2) led to marked improvement in her QoL.

Case 2

Diagnosed with MS since 2009, the patient suffered several relapses, causing neuropathic pain in the extremities and a spastic ataxic gait disturbance. After beginning natalizumab, she experienced no further disease flare-ups. A relevant comorbidity was cervical spinal canal stenosis. Previous antispasticity treatment attempts with baclofen and tizanidine were not tolerated due to side-effects (dizziness, fatigue). During treatment with nabiximols, her pain 0–10 NRS score decreased and, accordingly, the tramadol dose was halved. The spasticity 0–10 NRS score decreased. Walking distance was gradually extended from 0.5 km to 1 km. Improvements were recorded in sleep patterns and in overall disability. She described her QoL as 'good' (Table 2).

Case 3

Further to a diagnosis of relapsing-remitting MS in 2005, the patient experienced numerous relapses with gait disturbances. Increased muscle tone in the legs and painful night spasms were particularly stressful, along with nocturnal urinary incontinence and urinary urgency. Self-medication with smoked cannabis in the past had led to a perceived improvement in symptoms. After starting nabiximols treatment the patient noted improvement in spasticity, pain, bladder dysfunction and sleep disturbances as measured by 0–10 NRS scores; and a resolution of nocturnal spasms. These changes were accompanied by improvement in her disability status (EDSS score) and subjective improvement in QoL (Table 2).

Case 4

After the patient experienced double vision for the first time in 2004, there was suspicion of a chronic inflammatory central nervous system disease. In 2016, she had relapse events with sensitive paraplegic symptoms and an unsteady gait. In 2018, she was diagnosed with active secondary progressive MS with increasing paraparesis and decreasing walking ability. Comorbidities were a spastic-atactical gait disorder, pain in the knee joints due to knee injuries and chronic low back pain. The patient was taking baclofen 15 mg/day for spasticity. Chronic analgesic medication was considered unsuitable because of possible side effects. During nabiximols treatment, she perceived a decrease in pain severity from moderate to mild, especially in the knees and lower back, and to a lesser extent, an improvement in spasticity. Her sleep was better, and her disability status improved (Table 2).

Case 5

The patient had a 32-year history of MS-related spasticity and had been receiving tizanidine and baclofen in combination since 2005 as well as intrathecal triamcinolone acetate several times a year since 2010. Treatment was inadequate as spasticity and related symptoms continued to be moderate to severe. The patient experienced side effects (dizziness and fatigue) at the start of nabiximols treatment but persevered after perceiving improvement in spasticity along with a significant reduction in spasm frequency (from >100 to <10 per day), pain severity and daytime sleepiness. Adverse effects were minimal after 6 weeks and were absent after 23 weeks. Bladder function and subjective QoL were significantly improved (Table 2).

Case 6

The patient had primary progressive MS and a 21-year duration of MS spasticity. She had been treated with baclofen, tolperisone and tizanidine in combination since 2005. Spasticity in her legs and spasticity-related pain were severe. Her mobility was considerably impaired, limited to a walking distance of 2-5 m. During 9 years of treatment with nabiximols, spasticity in the patient's hands and legs was reduced. Importantly, tolperisone, which is no longer recommended for use in MS spasticity, could be discontinued. Improvements were recorded in walking distance and in pain, sleep and EDSS scores. Accordingly, the patient's QoL was greatly improved (Table 2).

Case 7

The patient had an 11-year history of MS spasticity and had been receiving baclofen and tizanidine in combination since 2017, along with intrathecal triamcinolone several times per year. Her spasticity and related sleep disorder were both severe (0–10 NRS scores of 8–10). A first attempt at treatment with nabiximols was unsuccessful as proper instructions on application technique (e.g. frequency, pause between each spray, alternate between spots in the mouth/mucosa) had not been provided. The error was corrected and, at her second attempt, she perceived noticeable improvement in leg spasticity after 8 weeks of use. Throughout 3 years of treatment with nabiximols, spasticity severity was reduced, spasms were absent (reduced from 100/day before treatment), and walking distance increased. Improvements were also present in pain severity, bladder function and sleep quality. Disability status (EDSS) was marginally improved and subjective QoL was better. Baclofen and triamcinolone could be discontinued (Table 2).

Case 8

This 60-year-old patient had a 15-year history of MS spasticity. Antispasticity medications included baclofen, tolperisone, tizanidine and intrathecal triamcinolone. Spasticity and associated symptoms were severe. He began treatment with nabiximols oromucosal spray but his response was limited. Changes made to administration times and dosages were unsuccessful. Nevertheless, the patient wished to continue treatment. After about 6 months, he stopped nabiximols at his own initiative due to a perceived lack of appreciable improvement in spasticity and associated symptoms. Pain and sleep disorder 0–10 NRS scores were reduced somewhat, whereas the bladder dysfunction 0–10 NRS score, walking distance and EDSS score were unchanged (Table 2). The patient also experienced adverse effects (dizziness, apathy and nightmares) during nabiximols treatment, which subsided about 2 months after stopping treatment.

Case 9

This patient (32 years) had a 3-year history of MS spasticity that was treated with baclofen and tizanidine.

Spasticity and related symptoms of pain, mobility impairment and sleep disorder were severe. During add-on treatment with nabiximols for 10 months, considerable improvements were recorded in spasticity, pain, bladder function, walking distance and sleep, the latter of which was aided by emphasizing the evening dose. Tizanidine was able to be discontinued, which improved her daytime function (Table 2).

Case 10

This patient was diagnosed with MS in 1987 and developed spasticity in 1995. He was treated with baclofen, tolperisone, tizanidine and intrathecal triamcinolone. All symptomatology except bladder dysfunction (none) was severe. At first use of nabiximols, the patient was not properly instructed in the application technique (see Case 7) and treatment was discontinued after about 3 months. Following correct instruction and monitoring, he had been receiving nabiximols for more than 5 years at the time the case report was prepared. Tolperisone and tizanidine could be discontinued. Meaningful improvements were recorded in spasticity severity and associated symptoms of spasms, pain and sleep impairment. The patient was able to stand better, with associated improvement in rollator-aided walking and wheelchair transfer ability (Table 2).

Case 11

This 26-year-old patient had a 5-year history of MS and a 3-year history of MS spasticity, which was treated with baclofen and tizanidine. Her spasticity was severe and was associated with significant mobility impairment. Walking distance was 5–10 m with assistance. Nabiximols treatment was initiated and maintained for 2 months at the maximum dose of 12 sprays/day without response (Table 2). The patient suffered a fall, which was considered to be nabiximols related. Nabiximols was discontinued.

Case 12

This 48-year-old patient with a 6-year history of MS spasticity was receiving baclofen, tizanidine, intrathecal triamcinolone and gabapentin. MS and related symptoms (spasms, pain, bladder dysfunction, sleep disorder) were all severe and her walking ability was limited to a few steps. During nabiximols treatment for 20 months, the patient's spasticity improved marginally, whereas significant improvement occurred in pain and sleep disorder which, in her view, greatly enhanced her QoL (Table 2).

Discussion

This case series describes 12 patients with moderate-to-severe MS spasticity who had failed to gain adequate symptomatic relief with conventional antispasticity medication and presented a range of spasticity-related symptoms. Together with a clinically important improvement in spasticity severity in 8 patients, add-on nabiximols was associated with improvements in spasms frequency and severity, pain, sleep disturbances, bladder function and walking distance in most patients. In common with other analyses exploring the effects of nabiximols on spasticity-associated symptoms,[16,17] meaningful amelioration of symptoms was observed irrespective of whether patients achieved ≥20% or ≥30% NRS improvement in spasticity severity.

Of note was the reduction in pain severity across all patients (except for the nabiximols non-responder), which is supported by other reports of nabiximols in MS-associated pain.[19,20] In the post-approval SAVANT clinical trial of patients with MS spasticity, nabiximols significantly reduced mean pain NRS scores compared with placebo (p=0.0013).[19] Randomized clinical trials of patients with MS-associated neuropathic pain reported mainly positive reductions in 0–10 pain NRS scores with nabiximols.[20]

The increase in walking distance observed in 8 of the 12 patients is consistent with other studies of nabiximols that investigated walking outcomes. Three-dimensional gait analysis in 20 patients with MS spasticity showed that nabiximols significantly improved speed, cadence and stride length.[21] Another group using three-dimensional gait analysis showed that the positive effects on balance and walking after an initial dose of nabiximols were maintained after 4 weeks of treatment.[22]

Mild or moderate dizziness is a common adverse event in patients receiving nabiximols oromucosal spray and typically occurs within the first few weeks of treatment.[7] This was observed in one patient (Case 5), who also reported fatigue. With continued use of nabiximols, the adverse effects subsided and the patient was able to benefit from an improvement in spasticity-related symptoms. In view of the limited number of treatment options for patients who fail to respond to nabiximols, pursuing a reasonable trial of therapy (e.g. 8 weeks) in patients with early tolerability issues might be a useful strategy provided that the side effects are tolerable. Conversely, Cases 8 and 11 are examples of patients who arguably should have discontinued nabiximols sooner. The patient in Case 8 reported a worsening in his health-related QoL due to prolonged adverse effects and a perceived lack of effectiveness, yet he chose to persevere with nabiximols for 6 months. The patient in Case 11, who had previously failed high-dose baclofen (80 mg/day) and tizanidine (20 mg/day), was also a nabiximols non-responder; she suffered a fall due to

dizziness at 7 weeks and treatment was terminated. Up to half of patients who begin nabiximols treatment may not achieve a level of symptomatic improvement sufficient to warrant continued treatment.[7]

As with all case series, the main limitation is the absence of a control group, and consequently no 'correction' for a possible placebo effect with patient-rated outcomes or for rater bias with clinician-reported outcomes. The small sample size warrants caution in terms of generalizing the results to a broader population. Changes to medicines used to manage spasticity-associated symptoms before and after nabiximols were not well documented and have not been presented. As the report reflects actual clinical practice, certain outcomes (e.g. health-related QoL) were not assessed formally using validated instruments. Case report forms were completed using a mixture of retrospective data (chart review) and contemporaneous data at the time of clinic visit. We acknowledge the potential for bias in our case selection; however, in order to examine outcomes at a granular level, it was necessary to identify patient records with a complete data set. The limitation of missing data that is common with retrospective chart review was largely overcome by using pro forma case report forms to capture patient details; however, in instances where clinical details prior to nabiximols were not recorded in medical charts, patients were asked to recall their symptom severity and assign a rating retrospectively.

Conclusions

This case series of patients with MS spasticity and variable spasticity-related symptoms shows that treatment with nabiximols oromucosal spray improved spasticity and spasticity-related pain in 11 of 12 patients (1 patient was a non-responder) and improved spasticity-related mobility impairment, bladder dysfunction and sleep disturbances in most patients. The series shows, at an individual level, that the benefits of nabiximols extend beyond spasticity to include spasticity-related symptoms. Nabiximols may have scope for broader use beyond spasticity in patients with MS and spasticity-associated symptoms.

Data availability statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Contributions: NG and MH have contributed to the conception, design or acquisition of data, or analysis and interpretation of data. All authors have participated in drafting, reviewing and/or revising the manuscript and have approved its submission. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole and have given their approval for this version to be published.

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