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Cannabinoids for spasticity in patients with multiple sclerosis: A systematic review and meta-analysis

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Abstract

Background: One of the most disabling symptoms of patients with multiple sclerosis (MS) is spasticity which affects their quality of life. Nowadays, cannabinoids are used for spasticity control in patients with MS, while the efficacy and safety are not clearly understood. So, we designed this systematic review and meta-analysis to assess the efficacy of cannabinoids for controlling MS-related spasticity.

Methods: PubMed, Scopus, EMBASE, Web of Science, and Google Scholar were systematically searched by two independent researchers on 1 May 2023. They also searched gray literature (references of included studies, as well as conference abstracts).

Results: A literature search revealed 6552 records, 95 full-texts were evaluated, and finally, 31 studies remained for systematic review. Among included studies, six randomized trials were included. Nabiximols was the most commonly used medication for controlling MS-related spasticity. Mean Expanded Disability Status Scale ranged between 4.6 and 7. Most studies (17 studies) were done in Italy, followed by Germany (4 studies). The pooled standardized mean difference (SMD) of NRS (Numeric Rating Scale) (after–before) is estimated as −1.41 (95% confidence interval (CI): −1.65, −1.17) ($I^2 = 97\%$, $p < 0.001$). The pooled standardized mean difference (SMD) of Ashworth (after-before) is estimated as −0.39 (95% CI: −0.72, −0.06) ($I^2 = 69.9\%$, $p = 0.005$).

Conclusion: The results of this systematic review and meta-analysis showed that nabiximols was the most common cannabinoid which was used to control MS-related spasticity, and it was effective in controlling MS-related spasticity (significantly decreased SMD of NRS, and Ashworth after treatment).

Keywords: Multiple sclerosis, spasticity, cannabinoids

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Introduction

Multiple sclerosis (MS) is a chronic disabling disease of the central nervous system (CNS), characterized by demyelinating plaques, and significant physical complications such as walking difficulties, gait imbalance, and spasticity.[1,2]

One of the most disabling symptoms of patients with MS is spasticity, affecting more than half of the patients, while literature shows that near three-fourths of affected individuals suffer from spasticity 15 years after disease progression.[3] Muscle hypertonia, stiffness, weakness, and following insomnia will result in interfering with daily activities, and quality of life impairment.[4]

The common treatment includes antispastic medications such as baclofen, tizanidine, or dantrolene in combination with physiotherapy, with not always fully satisfactory effects.[3,5] Withdrawal is common as the side effects include falling, sedation, dizziness, and withdrawal syndrome.[6]

Currently, Onabotulinumtoxin (BOTOX®, Allergan, Inc., Irvine, CA) injection has become more popular for controlling spasticity, but the duration of action is short, and administration of botox needs a high rate of specialization.[7,8]

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These days, people with MS admit to consuming cannabinoids to control different symptoms such as pain, anxiety, spasticity, and sleep disturbances.[9]

Cannabis is cultivated all over the world, containing over 483 identifiable chemicals, while only 80 cannabinoids are isolated from the plant, but the most famous ones are tetrahydrocannabinol (THC) and cannabidiol (CBD).[10]

Novotna et al.[11] for the first time introduced the application of oral spray of cannabinoids for MS-related spasticity, and nabiximols has been approved for MS-related spasticity treatment.

Various studies show that cannabinoids are used for spasticity control in patients with MS, while the efficacy and safety are not clearly understood. So, we designed this systematic review and meta-analysis to assess the efficacy of cannabinoids for controlling MS-related spasticity.

Methods

We followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 for reporting our systematic review, and meta-analysis.[12]

Eligibility criteria

Inclusion criteria: We included trials and observational studies that evaluated the effects of cannabinoids on spasticity in patients with MS.

Exclusion criteria: Case reports, case series, letters to editors.

We excluded studies that had no clear data for meta-analysis.

Information sources

PubMed, Scopus, EMBASE, Web of Science, and Google Scholar were systematically searched by two independent researchers on 1 May 2023. They also searched gray literature (references of included studies, as well as conference abstracts).

Search strategy

((Cannabinoids[MeSH Terms]) OR (Cannabis[MeSH Terms])) OR (Dronabinol[MeSH Terms])) OR (Nabilone[MeSH Terms])) OR (Cannabidiol[MeSH Terms])) OR (Phytocannabinoids[MeSH Terms])) OR (Nabiximols[MeSH Terms])) OR (Cannabinol[MeSH Terms])) OR (Cannabigerol[MeSH Terms])) OR (Cannabichromene[MeSH Terms])) OR (Cannabinoid*[Text Word])) OR (Cannabis[Text Word])) OR (Cannabi[Text Word])) OR (Hemp Plant*[Text Word])) OR (Plant, Hemp[Text Word])) OR (Plants, Hemp[Text Word])) OR (Marihuana[Text Word])) OR (Marijuana[Text Word])) OR (Cannabis indica[Text Word])) OR (Cannabis sativa[Text Word])) OR (Hemp*[Text Word])) OR (Hashish*[Text Word])) OR (Bhang*[Text Word])) OR (Ganja*[Text Word])) OR (Dronabinol[Text Word])) OR (9-ene-Tetrahydrocannabinol[Text Word])) OR (9 ene Tetrahydrocannabinol[Text Word])) OR (THC[Text Word])) OR (Tetrahydrocannabinol[Text Word])) OR (Tetrahydrocannabinol, (6a-trans)-Isomer[Text Word])) OR (Tetrahydrocannabinol, Trans-Isomer[Text Word])) OR (Tetrahydrocannabinol, Trans Isomer[Text Word])) OR (Marinol[Text Word])) OR (Tetrahydrocannabinol, (6aR-cis)-Isomer[Text Word])) OR (Nabilone[Text Word])) OR (nabilone, (6aR-trans)-isomer[Text Word])) OR (Cesamet[Text Word])) OR (Lilly 109514[Text Word])) OR (LY 109514[Text Word])) OR (nabilone, (6aS-trans)-isomer[Text Word])) OR (Cannabidiol[Text Word])) OR (Epidiolex[Text Word])) OR (Phytocannabinoid*[Text Word])) OR (Nabiximol*[Text Word])) OR (tetrahydrocannabinol-cannabidiol combination[Text Word])) OR (GW 1000[Text Word])) OR (GW1000[Text Word])) OR (GW-1000[Text Word])) OR (SAB 378[Text Word])) OR (SAB378[Text Word])) OR (SAB-378[Text Word])) OR (Sativex[Text Word])) OR (Cannabinol[Text Word])) OR (Cannabigerol[Text Word])) OR (Cannabichromene[Text Word])) AND ((((((((((((Multiple sclerosis[MeSH Terms]) OR (Muscle Spasticity[MeSH Terms])) OR (Multiple sclerosis[Text Word])) OR (Disseminated sclerosis[Text Word])) OR (Sclerosis, disseminated[Text Word])) OR (Sclerosis, Multiple[Text Word])) OR (Multiple Sclerosis, Acute Fulminating[Text Word])) OR (Muscle Spasticity[Text Word])) OR (Spasticity, Muscle[Text Word])) OR (Spastic[Text Word])) OR (Clasp-Knife Spasticity[Text Word])) OR (Clasp Knife Spasticity[Text Word])) OR (Spasticity, Clasp-Knife[Text Word]))

Selection process and collection

After the primary search, the obtained results were imported to ENDNOTE software. Duplicates were deleted, then titles and abstracts of eligible studies were assessed. Potential full texts were obtained, and were evaluated by two independent researchers.

Researchers extracted data and entered it in separate Excel files. If discrepancies were present, the third one solved the issue.

Data items

The first author of the publication, country of the study, publication year, duration of the study, number of study participants, total female, and male cases, type of MS, cannabinoid type, mean age at disease onset, mean Expanded Disability Status Scale (EDSS), type of the disease, numeric rating scale for spasticity, and Modified Ashworth Scale were extracted from included studies.

Study risk of bias assessment

ROBINS-I tool was used for Quality assessment of nonrandomized studies, while ROB2 was applied for quality assessment of randomized trials.[13,14]

Effect measures

We calculated standardized mean difference (SMD) for NRS, and Ashworth scale.

Synthesis methods

All statistical analysis was done using STATA (Version 14.0; Stata Corp LP, College Station, TX, USA). The p-values <0.05 were considered significant.

Certainty assessment

For all estimated effect sizes, we reported 95% CI. For studies that reported more than one endpoint outcome, we considered the final one.

Results

A literature search revealed 6552 records, 95 full-texts were evaluated, and finally, 31 studies remained for systematic review (Figure 1).

Included studies published between 2002 and 2023. Most studies were done in Italy, followed by Germany.

The number of patients in studies ranged between 8 and 1845, and the duration of studies ranged between 4 weeks and 1 year. Among included studies, six randomized trials were included. Except for four studies, all others used nabiximols. Mean EDSS ranged between 4.6 and 7. Most studies (17 studies) were done in Italy, followed by Germany (4 studies) (Table 1).

The quality assessment of trials and observational studies are summarized in Tables 2 and 3.

The pooled SMD of NRS (after–before) is estimated as −1.41 (95% CI: −1.65, −1.17) ($I^2 = 97\%$, $p < 0.001$) (Figure 2), indicating that cannabis use is effective in decreasing numeric rating scale of spasticity in patients with MS.

The pooled SMD of Ashworth (after–before) is estimated as −0.39 (95% CI: −0.72, −0.06) ($I^2 = 69.9\%$, $p = 0.005$) (Figure 3), indicating that cannabis use helps reducing Ashworth spasticity scale in patients with MS.

Discussion

To our knowledge, this is the first systematic review and meta-analysis in this field. According to our results, the administration of cannabinoids for controlling spasticity in patients with MS is helpful as the pooled SMD of NRS and Ashworth were significantly improved after administration of these medications. As our results show, the SMD of Ashworth scale was −1.78, which showed a great impact of cannabinoids on MS-related spasticity.

In a multicentric observational study, Guger et al. enrolled patients with MS who suffered from spasticity, and evaluated spasticity-treatment using nabiximols oromucosal spray. Their results showed near 40% reduction in NRS for spasticity after administration of the medication.[43]

In a single-center study, Sartori et al., evaluated the effects of botulinum toxin injections (BTI), and nabiximols on MS-related spasticity in patients with MS. Their results showed that BTI was more effective than nabiximols in treating MS-related spasticity.[27]

Vecchio et al., evaluated the effects of cannabinoids (cannabinoid spray) on spasticity in patients with MS. Participants were allowed to use the maximum dose of 12 puffs per day. They found that after 6 weeks, pain, and spasticity were improved significantly.[15]

Among included studies, some found that cannabinoids are not effective in controlling spasticity, while others did find. The difference among the findings is due to different inclusion and exclusion criteria, diverse definitions of spasticity, and follow-up duration variation.

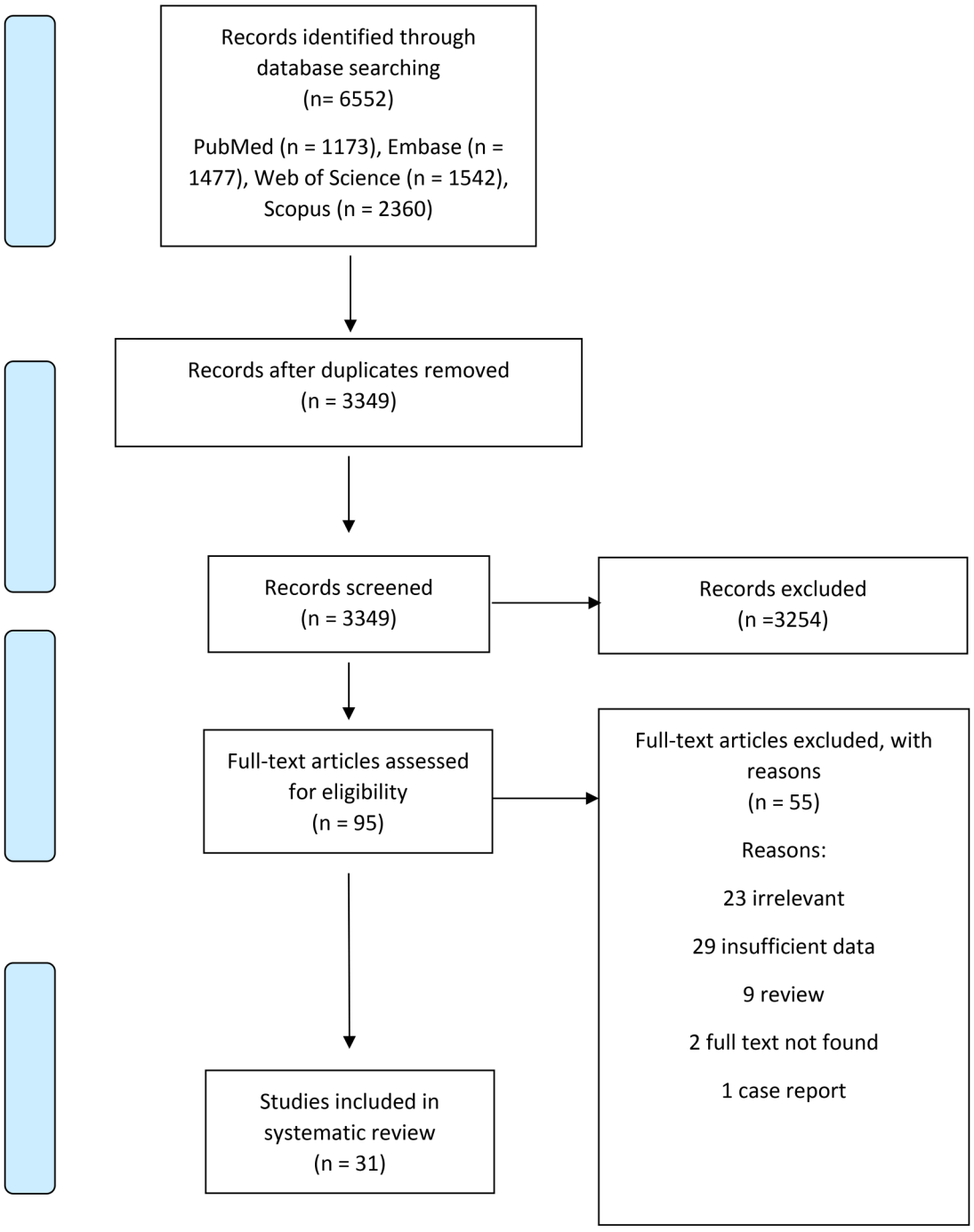

Figure 1. The flow chart of studies inclusion.

The first large-scale clinical trial to evaluate the effects of cannabinoids on MS-related spasticity was developed by Zajicek et al. in 2005, and 630 patients were recruited.

They were assigned to oral cannabis extract, Δ9-tetrahydrocannabinol, or placebo.

They reported improvement in spasticity as 61% in the first group, 60% in the second group, and 46% in the placebo group. We did not include this study as they reported a mean change of Modified Ashworth Scale for spasticity not crude numbers.[46]

Patients with MS suffer from spasticity based on demyelinating plaques of CNS, and damage to descending spinal pathways (corticospinal, reticulospinal, and vestibulospinal).[47] Factors such as male

Table 1. Included study (design and results).

Author	Year	Country	Study design	Study population	Age	Gender	Cannabinoid type	Study duration	Disease duration	EDSS	Disease type	Age at diagnosis	NRS: numeric rating scale for spasticity		Modified Ashworth Scale	
													Before	After	Before	After
Vecchio et al. [15]	2020	Italy	Nonrandomized trial	15	55.5 ± 5.2	11 F, 4 M	Nabiximols	6 weeks	17.4 ± 6.2	Median (range) 6 (2–8)	All progressive		Median (range) 5 (1–10)	Median (range) 2 (0–8)	Median (range) 14 (4–32)	Median (range) 4 (1–16)
Koehler et al. [16]	2013	Germany	Observational study	166		69 F, 97 M	Nabiximols	9 months			133 SPMS, 20 PPMS, 13 RRMS		Mean (range) 7 (4–10) (N = 120)	Mean (range) 3 (0–6) (N = 120)		
Collin et al. [17]	2010	UK	Double-blind, randomized, placebo-controlled, parallel-group study	337 (experiment: 167/ control: 170)	Experiment: 48 ± 10.06/Control: 47.1 ± 10.15	Experiment: 106 F, 61 M/control: 101 F, 69 M	Nabiximols	15 weeks	Experiment: 14.4 ± 8.29/ control: 16 ± 8.48	Experiment: 6 ± 1.56/control: 6 ± 1.50			Mean (SE) experiment: 6.77 (0.14) control: 6.49 (0.09)	Mean (SE) experiment: week 2: 6.16 (0.10) week 4: 5.81 (0.14) week 6: 5.59 (0.18) week 8: 5.49 (0.14) week 10: 5.35 (0.15) week 12: 5.36 (0.18) week 14: 5.34 (0.18) control: week 2: 5.96 (0.09) week 4: 5.73 (0.14) week 6: 5.64 (0.14) week 8: 5.70 (0.14) week 10: 5.75 (0.16) week 12: 5.59 (0.15) week 14: 5.58 (0.13)		
Squintani et al. [18]	2016	Italy	Nonrandomized trial	19	56.1 ± 8.9	14 F, 5 M	Nabiximols	4 weeks	17.6 ± 11.3	6.1 ± 1.4					1.1 ± 0.6	0.7 ± 0.5
Freidel et al. [19]	2014	Germany	Observational study	33	48.1	21 F, 12 M	Nabiximols	6 weeks		4.6			Mean, median (Q1, Q2,Q3, Q4) 6.03, 6 (3,5,7,10)	Mean, median (Q1,Q2, Q3,Q4) 3.61, 3 (1,2,5,7)		
Marinelli et al. [20]	2016	Italy	Nonrandomized trial	36	53.77 ± 10.32	21 F, 15 M	Nabiximols	4 weeks	181.28 ± 87.62 months	6.83 ± 0.55	29 SPMS, 6 PPMS, 1 RRMS		6.8 ± 1.7	5.7 ± 2.1		
Patti et al. [21]	2015	Italy	Cohort study	1615	51 ± 9.5	849 F, 766 M	Nabiximols	24 weeks	17.5 ± 8.6	Median (range) 6.5 (1.5–9.5)			7.5 ± 1.4 (N = 1597)	Week 4: 5.9 ± 1.6 (N = 1432) week 12: 5.1 ± 1.6 (N = 889) week 24: 4.8 ± 1.7 (N = 593)		
Vaney et al. [22]	2004	Switzerland	Randomized, double-blind, placebo-controlled cross-over parallel group study	57	54.9 ± 10	29 F, 28 M	Cannabis extract	31 days (14 treatment, 3 washout, 14 placebo)	17 ± 8.4	Median 7					Treatment period: 12.2 ± 6.4 Placebo period: 13.1 ± 6.3 (N = 50)	Treatment period: 11.6 ± 6.5 Placebo period: 11.5 ± 6.1 (N = 50)
Centonze et al. [23]	2009	Italy	Non randomized trial	20		13 F, 7 M	Nabiximols	6 weeks					5.36 ± 1.69	Week 1: 5.86 ± 1.98 Week 2: 5.85 ± 2.5 Week 3: 5.73 ± 2.48 Week 4: 5.56 ± 2.18 Week 5: 5.76 ± 2.1 Week 6: 5.71 ± 2.52	5.14 ± 2.12	Week 1: 5.11 ± 2.12 Week 2: 4.91 ± 2.01 Week 3: 4.97 ± 1.94 Week 4: 4.94 ± 2.02 Week 5: 5.14 ± 1.97 Week 6: 4.91 ± 1.98
Paolicelli et al. [24]	2016	Italy	Cohort	102	48.8 ± 10.4	52 F, 50 M	Nabiximols	40 weeks	19.2 ± 8	6.7 ± 1.1	59 SPMS, 25 RRMS, 10 PPMS, 8 PRMS		8.7 ± 1.3	Month 1: 6.2 ± 1.8 Month 3: 5.9 ± 1.6 Month 6: 6.1 ± 1.4 Year 1: 6.2 ± 1.4		
Flachenecker et al. [25]	2014	Germany	Observational, prospective, multicenter, noninterventional study	52	49.4 ± 8.6	29 F, 23 M	Nabiximols	1 year	14.1 ± 8.0	Median (range) 6 (3–8)	34 SPMS, 10 RRMS, 8 PPMS		6.2 ± 1.8	4.6 ± 2.1 (N = 51)		
Flachenecker et al. [26]	2014	Germany	Observational, prospective, multicenter, noninterventional study	276	50.0 ± 9.4	168 F, 108 M	Nabiximols	3 months	15.4 ± 9.0	Median (range) 6 (1–9)	168 SPMS, 72 RRMS, 34 PPMS, 2 PRMS		6.1 ± 1.7	Week 4: 5.2 ± 1.9 (N = 210)	3.0 ± 0.8	Week 4: 2.7 ± 0.9 (N = 260) Week 12: 2.6 ± 1.0 (N = 95)
Sartori et al. [27]	2021	Italy	Retrospective single-center study	36	53.9 ± 8.7	18 F, 18 M	Nabiximols		Median (range) 178 (8–447) months	Median (range) 6.75 (2.5–9)	19 SPMS, 9 RRMS, 8 PPMS				Median (range) 2 (0–4)	Median (range) 2 (0–4)
Chisari et al. [28]	2020	Italy	Prospective observational multicenter	1845	50.9 ± 12.3	1226 F, 619 M	Nabixomols	18 months	16.3 ± 8.8	Median (Range) 6.5 (4–8.5)	1283 SPMS, 333 PPMS, 229 RRMS	35.9 ± 11.7	7.8 ± 1.7	Week 4: 5.7 ± 1.6 (N = 1502) Month 3: 5.2 ± 1.4 (N = 1241) Month 6: 5.0 ± 1.7 (N = 1017) Month 12: 4.8 ± 1.8 (N = 853) Month 18: 4.7 ± 2.0 (N = 777)		
Lus et al. [29]	2018	Italy	Open-label, prospective, multicenter, nonpharmacological, randomized, minor interventional, postmarketing authorization pilot project	52	51.9 ± 9.1	32 F, 20 M	Nabiximols (chewing gum, cold bottle)	4 weeks	13.2 ± 7.5	6.2 ± 1.4	27 SPMS, 12 RRMS, 11 PPMS, 2 PRMS		6.1 ± 2.2	5.4 ± 2.2 (N = 46)		
Novotna et al. [30]	2011	UK	Nonrandomized trial	331	49.1 ± 9.85	202 F, 129 M	Nabiximols	4 weeks	12.3 ± 7.49	6 ± 1.4			6.91 ± 1.25	3.9 ± 1.51		
Gustavsen et al. [31]	2020	Denmark	Observational study	28 (24 THC, 4 CBD)	50	21 F, 7 M	Cannabis oil (THC rich, CBD rich)	4 weeks	Median (range) 11 (1–28)	Median (range) 4.5 (2–9)	15 RRMS, 8 SPMS, 5 PPMS		Median (range) THC: 6 (1–10) CBD: 6 (4–8)	Median (range) THC: 2.5 (0–7) (N = 18) CBD: 2 (2–2) (N = 3)		
D'hooghe et al. [32]	2021	Belgium	Retrospective study	238			Nabiximols	12 weeks					8.1 ± 1.08	Week 4: 5.2 ± 1.85 (N = 229) Week 8: 4.6 ± 1.69 (N = 188) Week 12: 4.1 ± 1.78 (N = 96)		
Messina et al. [33]	2017	Italy	Observational study	1597	51	841 F, 756 M	Nabiximols	6 months	17.5 ± 8.6	Median (range) 6.5 (1.5–9.5)	1029 SPMS, 311 RRMS, 255 PPMS		7.5 ± 1.4	Month 1: 5.9 ± 1.6 Month 3: 5.1 ± 1.6 Month 6: 4.8 ± 1.7		
Serpell et al. [34]	2012	UK	Open-label trial	146	50 ± 9	94 F, 52 M	Nabiximols	52 weeks					Mean (SEM) 5.68 (0.22)	Mean (SEM) 3.85 (0.25)		
Corey-Bloom et al. [35]	2012	USA	Randomized, double-blind,	30	51 ± 8	19 F, 11 M	Smoked cannabis	2 weeks	8.5 ± 7.4	5.3 ± 1.5	20 SPMS, 10 RRMS				Mean (95%CI) treatment: 9.13	Mean (95%CI) treatment: 6.18 (5.13–7.21)

(continued)

Table 1. Continued.

Author	Year	Country	Study design	Study population	Age	Gender	Cannabinoid type	Study duration	Disease duration	EDSS	Disease type	Age at diagnosis	NRS: numeric rating scale for spasticity		Modified Ashworth Scale	
													Before	After	Before	After
			placebo-controlled crossover design												(8.21–10.07) placebo: 8.92 (8.03–9.79)	placebo: 8.71 (7.57–9.71)
Vermersch et al.[36]	2016	Italy	Observational study	433	50.4 ± 10.4	239 F, 194 M	Nabiximols	3 months	13.7 ± 7.9	5.94 ± 1.38	223 RRMS, 137 RRMS, 72 PPMS		6.9 ± 1.9 (N = 394)	5.3 ± 1.8 (N = 253)		
Maniscalco et al.[37]	2017	Italy	Observational study	15	56.1 ± 8.6	7 F, 8 M	Nabiximols	4 weeks	Median (range) 91 (4–276) months				Median (range) 8 (4–10)	Median (range) 6 (2–8)		
Carotenuto et al.[38]	2016	US	Nonrandomized trial	10	51.10 ± 9.96	10 F, 10 M	Nabiximols	1 year	Median (range) 9.21 (2–39)	4.70 ± 1.08	12 progressive, 8 relapsing	37.28 ± 13.61	8 ± 1.93 (N = 10)	5.50 ± 2.45 (N = 10)		
Coghe et al.[39]	2015	Italy	Nonrandomized trial	20	49.6 ± 9.11	11 F, 9 M	Nabiximol	1 month		5.3 ± 0.81	4 RRMS, 1 PRMS, 1 SPMS		7.1 ± 1.22	5.24 ± 1.39		
Ferrante et al.[40]	2019	Italy	Retrospective cohort study	37	56 ± 9	26 F, 11 M	Nabiximols						7.86 ± 1.00	5.66 ± 1.04		
Patti et al.[41]	2022	Italy	Observational study	1138	51.5 ± 9.8	621 F, 517 M	Nabiximols	18 month	19.8 ± 10.5	6.5 ± 1.16	761 SPMS, 193 RRMS, 183 PPMS		7.8 ± 1.25	Week 4: 5.9 ± 1.5 Month 3: 5.3 ± 1.3 (N = 760)Month 6: 5.1 ± 1.2 (N = 653) Month 12: 5.1 ± 1.2 (N = 473) Month 18: 5.1 ± 1.2 (N = 397)		
Pau et al.[42]	2023	Italy	Nonrandomized trial	13	51.2 ± 11.8	9 F, 4 M	Nabiximols	4 weeks		5.4 ± 1.6	11 SPMS, 1 RRMS, 1 PPMS		6.3 ± 1.3	4.2 ± 1.3		
Guger et al. [43]	2023	Austria	Prospective observational study	55	52.5 ± 9.6	33 F, 22 M	Nabiximols	3 month	15.1 ± 9.1	5.3 ± 1.3	28 SPMS, 18 PPMS, 9 RRMS		6.4 ± 1.8	Month 1: 4.8 ± 1.7 (N = 43) Month 3: 3.9 ± 2.0 (N = 40)		
Gajofatto et al.[44]	2023	Italy	Nonrandomized trial	12	Median (range) 51 (36–73)	5 F, 7 M	Nabiximols	8 weeks	Median (range) 21.5 (10–37)	Median (range) 6 (4.5–8)	10 SPMS, 2 RRMS		Median (range) 8 (5–9)	Median (range) 6.5(4–8)		
Killestein et al.[45]	2002	The Netherland	Randomized, double-blind, placebo-controlled, twofold crossover study	16 (each group 8)	46 ± 7.9		Dronabinol	4 weeks	15 ± 10.7	6.2 ± 1.2	10 SPMS, 6 PPMS				Placebo: 1.15 (0.94–1.37) plant extract: 1.20 (0.97–1.39) drobinidol: 1.13 (0.92–1.36)	Placebo: 1.03 (0.81–1.23) plant extract: 0.94 (0.74–1.14) drobinidol: 0.97 (0.77–1.18)

CBD: cannabidiol; EDSS: Expanded Disability Status Scale; F: female; M, male; NRS: Numeric Rating Scale; PPMS: primary progressive multiple sclerosis; PRMS: progressive-relapsing multiple sclerosis; RRMS: relapsing-remitting mustiple sclerosis; SE: standard error; SEM: standard error of the mean; SPMS: slowly progressive multiple sclerosis; THC: tetrahydrocannabinol.

Table 2. Quality assessment of nan-randomized studies (ROBINS-I).

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall Bias
Vecchio et al.[15]	Low	Low	Low	Low	Low	Low	Low	Low
Koehler et al.[16]	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate
Squintani et al.[18]	Low	Low	Low	Low	Low	Low	Low	Low
Freidel et al. [19]	Low	Low	Low	Low	Moderate	Low	Low	Moderate
Marinelli et al. [20]	Low	Low	Low	Low	Low	Low	Low	Low
Patti et al.[21]	Low	Low	Low	Low	Moderate	Low	Low	Moderate
Centonze et al.[23]	Low	Moderate	Low	Low	Low	Low	Low	Moderate
Paolicelli et al.[24]	Low	Low	Low	Low	Low	Low	Low	Low
Flachenecker et al.[25]	Low	Low	Low	Low	Moderate	Low	Low	Moderate
Flachenecker et al.[26]	Low	Low	Low	Low	Moderate	Low	Low	Moderate
Sartori et al.[27]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Chisari et al.[28]	Low	Low	Low	Low	Moderate	Low	Low	Moderate
Novotna et al.[30]	Low	Low	Low	Low	Low	Low	Low	Low
Gustavsen et al.[31]	Low	Low	Low	Low	Moderate	Low	Low	Moderate
D'hooghe et al.[32]	Low	Low	Low	Low	Moderate	Low	Low	Moderate
Messina et al.[33]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Serpell et al.[34]	Low	Low	Low	Low	Low	Low	Low	Low
Vermersch et al.[36]	Low	Low	Low	Low	Moderate	Low	Low	Moderate
Maniscalco et al.[37]	Low	Low	Low	Low	Low	Low	Low	Low
Carotenuto et al.[38]	Low	Moderate	Low	Low	Low	Low	Low	Moderate
Coghe et al.[39]	Low	Low	Low	Low	Low	Low	Low	Low
Ferrante et al.[40]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Patti et al.[41]	Low	Moderate	Low	Low	Moderate	Low	Low	Moderate
Pau et al.[42]	Low	Moderate	Low	Low	Low	Low	Low	Moderate
Guger et al.[43]	Low	Low	Low	Low	Moderate	Low	Low	Moderate
Gajofatto et al.[44]	Low	Moderate	Low	Low	Low	Low	Low	Moderate

Table 3. Quality assessment of randomized trials (ROB2).

Study	Randomization process	Deviations from the intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall bias
Collin et al.[17]	Some concerns	Low	Low	Low	Low	Some concerns
Vaney et al.[22]	Low	Low	Low	Low	Low	Low
Lus et al.[29]	Some concerns	Low	Some concerns	Low	Low	Some concerns
Corey-Bloom et al.[35]	Some concerns	Low	Low	Low	Low	Some concerns
Killestein et al.[45]	Low	Low	Some concerns	Low	Low	Some concerns

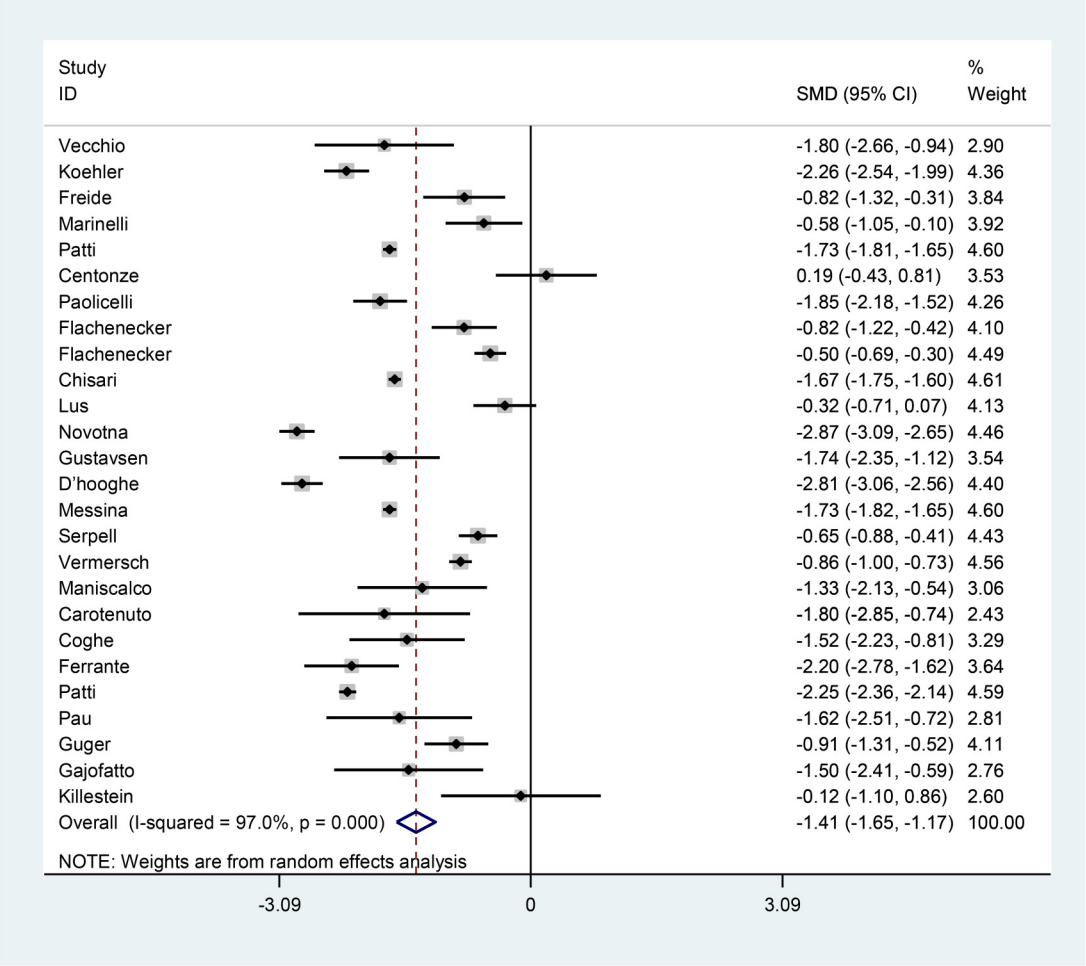

Figure 2. The pooled SMD of NRS (after–before). NRS: Numeric Rating Scale; SMD: standardized mean difference.

sex, duration of MS disease, higher level of disability, and relapses play roles in developing MS-related spasticity.

Urinary tract infections, distension of the urinary bladder and rectum, pain, and pressure sores could lead to development, and aggravation of spasticity in MS.[48]

The most common medication that is used for MS-related spasticity is baclofen followed by benzodiazepines, while their efficacy is not very satisfactory. Botulinum toxin type A is another medication that could reduce muscle tone, but it is partially effective.[48]

In animal models of MS, both endogenous and exogenous cannabinoids improve spasticity and tremors.[49]

Cannabinoids activate G protein-coupled receptors (GPCRs), leading to increased synthesis of cyclic

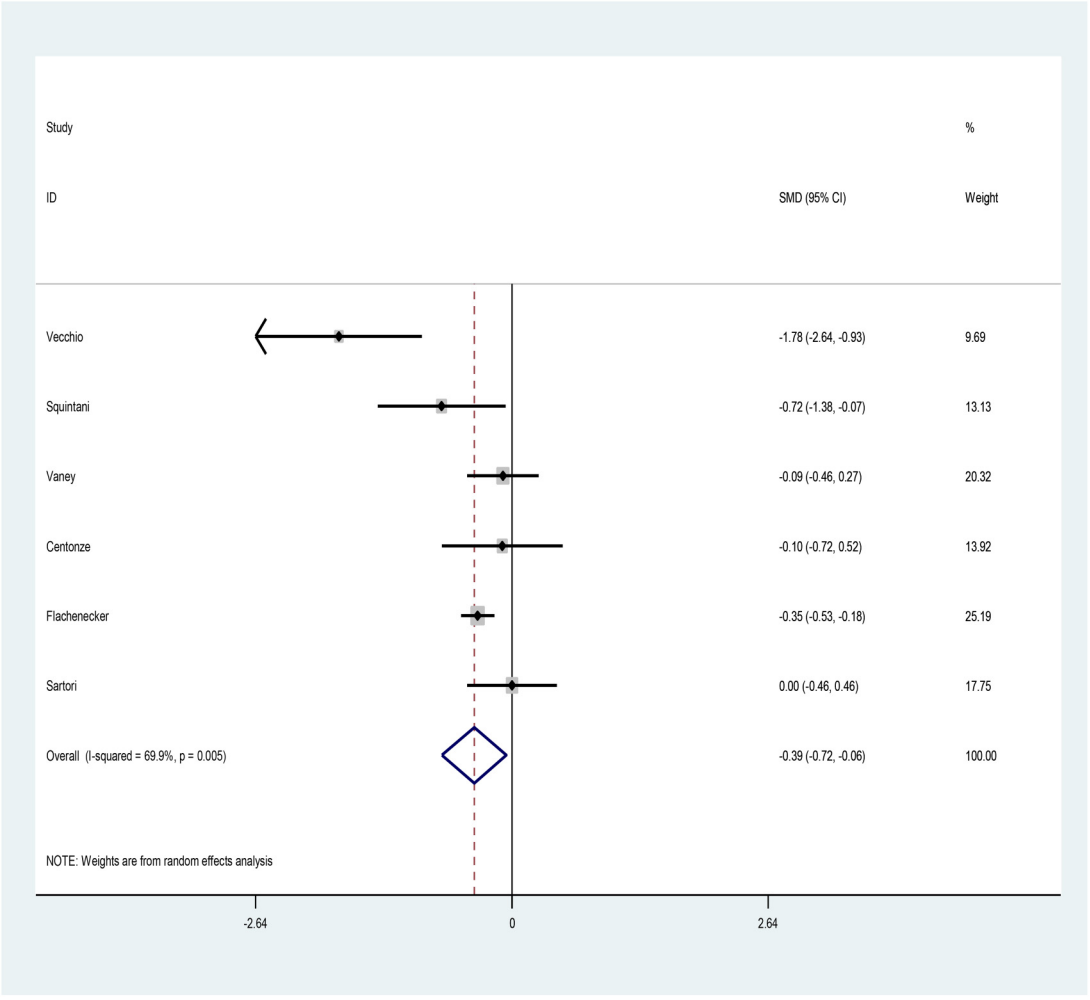

Figure 3. The pooled SMD of Ashworth (after–before). SMD: standardized mean difference.

adenosine monophosphate (cAMP), and activation of cAMP-dependent protein kinase (PKA) that helps phosphorylation of channel protein. All these effects result in ionic permeability modification.[50]

The administration of cannabinoids to control MS-related spasticity may help patients, but larger multicentric studies are needed.

This study had some limitations. First, the inclusion and exclusion criteria differed between included studies. Second, some studies applied NRS while others used Ashworth scale for spasticity evaluation. Third, the duration of disease differed between studies.

Conclusion

The results of this systematic review and meta-analysis showed that nabiximols was the most common cannabinoid which was used to control MS-related spasticity, and it was effective in controlling MS-related spasticity (significantly decreased SMD of NRS, and Ashworth after treatment).

Authors' contribution

MA was involved in conceptualization, investigation, writing—original draft, and writing—review & editing; MP in conceptualization, formal analysis, andwriting—review & editing; FG in investigation, data curation, and writing—review & editing; SZE-R in project administration, supervision, visualization, and writing—review & editing; ETB in visualization, data curation, and writing—review & editing; MG in methodology, software, formal analysis, and writing—original draft; and MR in methodology, software, formal analysis, and writing—original draft.

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