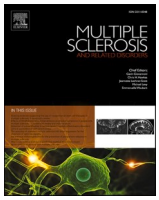
Multiple Sclerosis and Related Disorders 68 (2022) 104173

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard



Review article

Effects of Sativex® on cognitive function in patients with multiple sclerosis: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:
Nabiximols
Multiple sclerosis
Spasticity
Cognitive function
Systematic review
Meta-analysis

ABSTRACT

Background: Cognitive impairment is a common manifestation of multiple sclerosis (MS).
Objective: To assess by systematic review and meta-analysis available evidence regarding the impact of nabiximols oromucosal spray on cognition in patients with MS.
Methods: A systematic literature search of clinical studies (all types, any comparator) that measured cognitive function in patients with MS spasticity treated with nabiximols. Meta-analysis for cognitive endpoints was not possible due to heterogenous measurement instruments and outcomes. Meta-analysis was performed for adverse events (AEs) of special interest (cognition disorders) reported in randomized controlled trials (RCTs) of nabiximols versus placebo in patients with MS (with or without spasticity). Certainty of evidence and risk of bias were assessed.
Results: Seven clinical studies (three RCTs) directly assessing cognitive function were included in the qualitative analysis. There was no consistent evidence to suggest that nabiximols causes cognitive impairment as assessed by a range of specific psychometric instruments across cognitive domains. Thirteen double-blind, placebo-controlled RCTs (nabiximols, $n = 964$; placebo, $n = 904$) were included in the meta-analysis of cognitive AEs. Most cognitive AEs (30 of 32 events, 93.8%) reported with nabiximols in MS patients occurred with not in-label use, i.e., dosage >12 sprays per day and/or not administered primarily for treatment of spasticity.
Conclusions: Within the limitations of the review, we can conclude that no detrimental effects of nabiximols on cognitive function were observed in patients with MS spasticity during up to 12 months follow-up and that cognitive AEs were rare and occurred only when nabiximols was not used according to its approved label.

1. Introduction

Cognitive impairment is a common manifestation of multiple sclerosis (MS), affecting an estimated half to two-thirds of patients irrespective of disease duration, stage or subtype (Chiaravalloti and DeLuca, 2008; Oreja-Guevara et al., 2019). Inflammation, neuronal degeneration and lesion topography are among the likely causes leading to disruption of the cognitive network (Rocca et al., 2015). Although patterns of cognitive impairment in MS can vary widely, deficits are typically observed in the domains of attention, information processing speed, episodic memory, and executive functions (Chiaravalloti and DeLuca, 2008; Rocca et al., 2015), which appears to be due to disruption of complex brain networks subserving these dynamic and speed-related cognitive functions. Magnetic resonance imaging associates regional grey matter atrophy and neural network disruption with the presence of cognitive impairment (Benedict et al., 2020; Cruz-Gomez et al., 2021). Cognitive deficiencies can restrict a person's ability to perform daily activities, and may be predictive for a negative prognosis, a more aggressive pathology, and a decline in vocational status/employment, with associated detriment to personal and social functioning and quality of life (Chiaravalloti and DeLuca, 2008; Campbell et al., 2017; Kobelt et al., 2017; Pitteri et al., 2017; Povolo et al., 2019; Renner et al., 2020).

Cannabis and cannabinoids have been investigated in numerous neurological conditions, including MS (Abrams, 2018). The main active constituents of the *Cannabis sativa* plant, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), exert their effects by interacting with

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https://doi.org/10.1016/j.msard.2022.104173
Received 5 January 2022; Received in revised form 5 September 2022; Accepted 8 September 2022
Available online 14 September 2022

cannabinoid receptors (CB1 and CB2) in the endocannabinoid system (Pertwee, 2008). The pharmacological effects of cannabis are mediated mainly through THC-induced activation of CB1 receptors in brain regions associated with motor control, pain regulation, memory processing and psychoactivity (Vučković et al., 2018), whereas CBD behaves as a non-competitive negative allosteric modulator of CB1 receptors (Laprairie et al., 2015).

Acute and chronic exposure to cannabis is associated with dose-related cognitive impairment, particularly with respect to attention and working memory, as demonstrated in animals (Zanettini et al., 2011) and humans (Solowij and Battisti, 2008). There is supporting evidence to suggest that chronic recreational cannabis use in young people has detrimental effects on attention (Abdullaev et al., 2010; Hanson et al., 2010), spatial working memory (Kanayama et al., 2004), verbal learning and memory (Lisdahl et al., 2013), and executive functioning (Gonzalez et al., 2012; Grant et al., 2012). Higher doses and more intensive lifetime use of cannabis was also found to be associated with modest reductions in cognitive performance in older adults with or without neurocognitive disorders (Scott et al., 2019). However, these effects relate primarily to the use or abuse of inhaled recreational cannabis; it is uncertain whether the same applies to therapeutic use of cannabis-based medicines.

Given the inherent vulnerability of MS patients to cognitive impairment, the potential (negative) effects of cannabinoids on cognition are a concern (Chiaravalloti and DeLuca, 2008; Oreja-Guevara et al., 2019; Leussink et al., 2012). Some evidence suggests that administering CBD with THC may reduce the psychotropic effects of THC, owing to its THC-receptor modulating and neuroprotective properties (Russo and Guy, 2006). Co-administration of CBD may also substantially reduce the negative effects of THC on memory and cognition, emphasizing the importance of formulation when developing cannabinoid products for medicinal use (Russo and Guy, 2006).

Sativex (USAN: nabiximols) is a complex botanical product for oromucosal use to treat MS spasticity. Nabiximols is derived from the *Cannabis sativa* plant and contains a mixture of cannabinoid and non-cannabinoid plant components. The most abundant cannabinoids in nabiximols are THC and CBD which are standardized at concentrations of 27 mg/mL and 25 mg/mL, respectively; non-cannabinoid plant components include alpha- and trans-caryophyllenes, other terpenes, sterols, and triglycerides (Electronic Medicines Compendium 2021).

There is scarce evidence to date regarding the cognitive effects of medical cannabis, including nabiximols, in approved indications. Moreover, it is possible that the cognitive effects of cannabinoid-based medicines are sometimes confused with or reported together with co-existing psychiatric events and conditions. To the best of our knowledge no systematic literature review to date has focused specifically on cognition in patients with MS spasticity treated with nabiximols. This systematic review and meta-analysis was undertaken to assess available evidence regarding the impact of nabiximols treatment on cognitive functioning in patients with spasticity due to MS.

2. Methods

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines (Liberati et al., 2009) and Cochrane Handbook (Higgins et al., 2019).

2.1. Inclusion and exclusion criteria

Publication eligibility was defined using the Populations-Interventions-Comparators-Outcomes-Study Design (PICOS) framework (Table 1). Considered for inclusion were full-text articles or official study register reports of randomized controlled trials (RCTs), non-randomized clinical trials (N-RCT), prospective or retrospective non-interventional studies (NIS) and case reports that measured cognitive function in patients with spasticity due to MS who had been treated with nabiximols oromucosal spray or any comparator including placebo, or no comparator. Excluded from the primary analysis were studies in patients with spasticity due to conditions other than MS or studies in patients with MS but without spasticity, and studies without cognitive measurements or assessments. For additional analysis of cognitive AEs, all RCTs of nabiximols versus placebo in MS patients were included. Language was limited to English.

Table 1
Eligibility criteria to select studies for data extraction (primary search).

PICOS factors	Inclusion criteria	Exclusion criteria
Population	Patients with spasticity due to multiple sclerosis	Patients with spasticity due to any other condition than multiple sclerosis Patients with multiple sclerosis without spasticity
Intervention	Sativex (nabiximols) oromucosal spray	Any other cannabinoid
Comparison / Control	Any type of comparator, including placebo No comparator	(None)
Outcome	Cognitive function(s), any measurements or instruments	No cognitive measurements or assessments
Study design	All, any	(None)

Filters applied: any publication date, records in English, only full texts and reports in official study registers

2.2. Search strategy, selection and data collection

A comprehensive search strategy was developed for MEDLINE (PubMed) to identify clinical studies (all types) of nabiximols in patients with MS spasticity that reported cognitive endpoints. Sensitivity analyses were performed by means of two additional detailed searches, one for cognitive assessment instruments and the other for cognitive domains. The main PubMed search was supplemented by extended searches in other databases: CENTRAL (Cochrane Library; https://www.cochranelibrary.com); Epistemonikos (https://www.epistemonikos.org/); Physiotherapy Evidence Database (PEDro; https://search.pedro.org.au); and Google Scholar (https://scholar.google.com). Article titles retrieved from these queries were examined to exclude any clearly unrelated publications. Reference lists of original and review articles were searched manually to identify any other relevant articles. The search timeframe was from inception to 1 April 2021.

An additional search was conducted to identify RCTs of nabiximols versus placebo in patients with MS which reported AEs including AEs of special interest with nabiximols (clinically significant AEs, fall-related injury requiring medical attention, significant psychiatric or psychotic events, suicidal thoughts or attempted suicide, change in driving ability). Searches were conducted in ClinicalTrials.gov (https://clinicaltrials.gov), EudraCT (https://www.clinicaltrialsregister.eu), and PubMed (applying the 'clinical trials' filter) for studies published from inception to 1 April 2021. Article titles retrieved from these queries were examined to exclude any clearly unrelated publications. Reference lists of original and review articles were searched manually to identify any other relevant articles.

Systematic search details, excluded publications and reasons for exclusion are provided in Supplementary File 1.

EMBASE (https://www.embase.com) and PsychINFO (https://www.ebsco.com/de-de/produkte/datenbanken/apa-psycinfo) were not searched because access is not free.

Two reviewers (ID, UE) independently reviewed the records according to predefined inclusion/exclusion criteria and selected publications for inclusion; a third reviewer (IKP) resolved any disagreements.

2.3. Data extraction

The first reviewer (ID) abstracted and tabulated data from source publications into Microsoft Excel (Microsoft Corp) spreadsheets according to predefined fields. The second reviewer (UE) checked the extracted data for completeness and consistency against original sources.

Variables extracted from RCTs and NIS of nabiximols in patients with MS spasticity which reported cognitive assessment endpoints included: publication citation details, study details (design and description), population details (demographic characteristics and medical history), intervention details (nabiximols and comparators), concomitant therapy, outcomes (cognitive assessments, other assessments, safety and tolerability), and overall conclusions. Outcomes for cognitive assessments were classified and reported per domain: processing speed, executive function, verbal memory, visual memory, attention, visuospatial processing, and multiple domain screenings (Landmeyer et al., 2020). Full details are provided in Supplementary File 2.

Variables extracted from RCTs of nabiximols versus placebo in patients with MS which reported cognitive AEs included: publication citation details, study type, indication, sample size, number of patients, intervention, duration of use (weeks), maximum dosage (sprays), in-label use (yes/no), and cognitive and other AEs. Full details are provided in Supplementary File 3. In-label use of nabiximols was defined as use to treat MS spasticity at a dosage of ≤12 sprays per day as per approved labelling in Europe (Electronic Medicines Compendium 2021). Not in-label use of nabiximols was defined as a dosage >12 sprays/day and/or administered for a primary reason other than treatment of MS spasticity. Cognitive AEs were defined based on the clinical judgement of AEs reported in source publications as per system organ class (SOC), e.g., cognitive disorder, memory impairment, psychomotor skills impaired, and disturbance in attention. Any AEs of somnolence, sleep attacks, drowsiness and/or slower thinking, feeling drunk, disorientation, confusional state, dissociation, stupor, apathy, lethargy, hallucination, and euphoria and euphoric mood reported in source publications were considered to be psychological or psychiatric AEs.

2.4. Summary measures and statistical analyses

Meta-analysis was planned for cognitive function endpoints reported in studies of nabiximols in patients with MS spasticity (all types, all comparators), using baseline and study timepoint scores to compute where possible standardized mean difference (SMD; Hedges' g) effect size estimates across nabiximols and placebo administrations. Effect size was to be assessed according to Hedges' 'rule of thumb' (irrelevant difference = SMD < 0.2; small effect = SMD between 0.2 and 0.5; medium effect = SMD between 0.5 and 0.8; large effect = SMD > 0.8) (Hedges, 1981).

Meta-analysis was planned for cognitive AEs reported in RCTs of nabiximols versus placebo in patients with MS if the same cognitive AE or psychiatric AE was reported in two or more studies, using the odds ratio (OR) to evaluate the treatment effect on cognitive AEs. The confidence interval (CI) was set to 95%. Individual study effect sizes were inverse-variance weighted and pooled to produce an average nabiximols-induced effect and an average placebo-induced effect using a random effects model under a frequentist framework. Heterogeneity was assessed using the I^2 statistic, tau $(\tau)^2$ and Chi^2 test where a P-value of < 0.1 was considered significant. The I^2 statistic was assessed according to Cochrane Handbook recommendations (0% to 40% = might not be important; 30% to 60% = may represent moderate heterogeneity; 50% to 90% = substantial heterogeneity; 75% to 100% = considerable heterogeneity) (Deeks et al., 2020).

2.5. Quality of evidence assessment (GRADE)

In accordance with the Cochrane Collaboration Handbook (Higgins et al., 2020a), evidence quality of included studies was assessed by two authors (ID and UE) using GRADEpro GDT, the Cochrane Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool for RCTs (GRADE 2021).

2.6. Risk of bias assessment

Risk of bias in RCTs was assessed by two authors (ID and UE) using the revised Cochrane risk-of-bias tool (RoB 2) (Higgins et al., 2020b). Each included RCT was evaluated for literature quality including the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, selection of reported result and overall bias. Each RCT was classified as having high, low, or unclear risk for the abovementioned items. If one item was classified as high risk, the overall assessment was classified as high risk. Risk of bias in NIS was planned to be assessed by the same two authors using the ROBINS-I tool (Sterne et al., 2016).

3. Results

3.1. Search results

A flow chart of the main literature search (cognitive endpoints in all types of studies of nabiximols in MS spasticity) and additional literature search (cognitive AEs in RCTs of nabiximols versus placebo in MS) shows the process of identifying relevant publications (Fig. 1).

Database searches for studies (all types) of nabiximols in MS spasticity which reported cognitive endpoints yielded 51 records, supplemented by one additional record identified through hand searching. After exclusion at screening and deduplication at eligibility assessment, seven full-text articles were included in the qualitative analysis (Wade et al., 2004; Aragona et al., 2009; Vachová et al., 2014; Russo et al., 2016; Castelli et al., 2019; Carotenuto et al., 2020; Alessandria et al., 2020).

Database searches for RCTs of nabiximols versus placebo in MS which reported cognitive AEs yielded 45 records, supplemented by three records identified through hand searching. After exclusion at screening and deduplication at eligibility assessment, 13 records (12 full text articles, one clinicaltrials.gov entry) were included in the qualitative analysis (Wade et al., 2004; Aragona et al., 2009; Vachová et al., 2014; Rog et al., 2005; Collin et al., 2007; Collin et al., 2010; Kavia et al., 2010; Notcutt et al., 2012; ClinicalTrials.gov 2012; Langford et al., 2013; Novotna et al., 2011; Leocani et al., 2015; Markovà et al., 2019), and 13 records (12 full text articles, one clinicaltrials.gov entry) were included in the quantitative analysis (Wade et al., 2004; Aragona et al., 2009; Vachová et al., 2014; Rog et al., 2005; Collin et al., 2007; Collin et al., 2010; Kavia et al., 2010; Notcutt et al., 2012; ClinicalTrials.gov 2012; Langford et al., 2013; Novotna et al., 2011; Leocani et al., 2015; Markovà et al., 2019).

3.2. Cognitive endpoints from studies (any type) of nabiximols in spasticity due to MS

Three double-blind, placebo-controlled RCTs (Wade et al., 2004; Aragona et al., 2009; Vachová et al., 2014), three single-center real-world studies (Russo et al., 2016; Castelli et al., 2019; Carotenuto et al., 2020), and one prospective single-blind observational study (Alessandria et al., 2020) of nabiximols in patients with MS spasticity reported cognitive endpoints (Table 2). Five of these studies evaluated cognition as a stated study objective (Aragona et al., 2009; Vachová et al., 2014; Russo et al., 2016; Carotenuto et al., 2020; Alessandria et al., 2020). Collectively, the studies enrolled 812 patients (range: 17 to 396), of whom 673 were treated with nabiximols. Patient populations had a female preponderance (55% to 65%), mean age across studies was about 50 years and, where reported, mean or median Expanded Disability Status Scale scores were around 6. Two studies reported previous

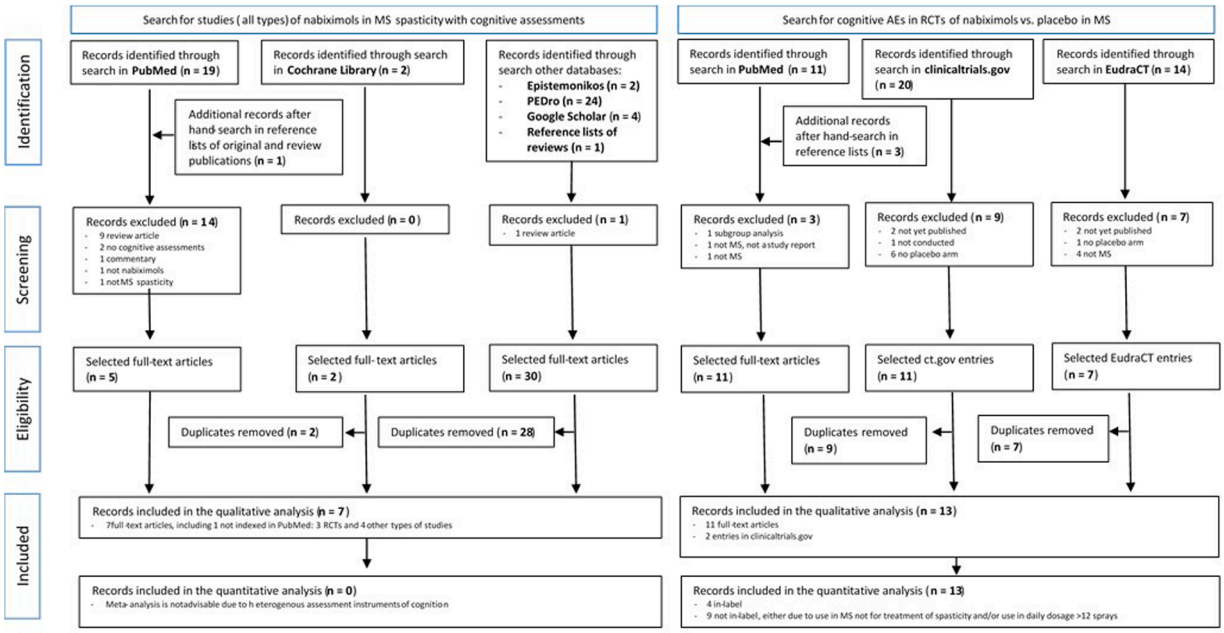

Fig. 1. PRISMA diagram.

medicinal cannabis use in around 40% of patients treated with nabiximols (Wade et al., 2004; Vachová et al., 2014), and one study reported previous recreational cannabis use in 16.3% of patients treated with nabiximols (Wade et al., 2004). Treatment duration across studies ranged from 3 weeks to 5.4 years. Cognitive assessment timepoints ranged from 3 weeks to 12 months.

GRADE-assessed quality of evidence was low due to uncertainties in consistency, directness, and precision domains (Table 3). Risk of bias was not assessed because of the impossibility of performing a quantitative analysis due to heterogenous cognitive measurement instruments and outcomes.

Outcomes for cognitive assessments by domain are provided in Table 2 and summarized descriptively below.

3.2.1. *Processing speed*

Five studies examined processing speed as a cognitive endpoint (Wade et al., 2004; Aragona et al., 2009; Vachová et al., 2014; Carotenuto et al., 2020; Alessandria et al., 2020). A 6-week RCT in patients with MS recorded no significant differences between nabiximols and placebo in the Adult Memory and Information Processing Battery (AMIPB) (Wade et al., 2004). Two studies reported no significant changes from baseline in the Paced Auditory Serial Addition Test (PASAT) (Aragona et al., 2009) or the Symbol Digit Modalities Test (SDMT) (Carotenuto et al., 2020). A RCT in patients with MS spasticity recorded similar improvements from baseline to 48 weeks in the adjusted mean PASAT total score for nabiximols and placebo, indicating non-inferiority of nabiximols versus placebo with regard to an effect on processing speed (Vachová et al., 2014). An observational pilot study involving 20 patients with MS spasticity found significant improvement from baseline in the SDMT with nabiximols at 6 months ($p < 0.001$) and 12 months ($p = 0.020$) but no changes in other measures of processing speed (PASAT-3 and PASAT-2) (Alessandria et al., 2020).

3.2.2. *Executive functions*

A real-world study that used the Trail Making Test (TMT) to assess executive functions found no changes from baseline with nabiximols at 4 weeks or 6 months (Russo et al., 2016). In an Italian real-world single-clinic study investigating postural control in 22 patients with MS, no difference compared with baseline was observed in the Stroop Color and Word Test (SCWT) after one, three and 12 months of nabiximols treatment under single task conditions, i.e., without application of the postural task (Castelli et al., 2019). Under dual-task conditions with simultaneous application of the cognitive test and postural task, the number of correct items on the SCWT decreased significantly at month 12 ($p = 0.025$ by post-hoc Bonferroni test).

3.2.3. *Verbal memory*

Real-world studies of nabiximols reported no significant changes from baseline in the Babcock Story Recall Test (BSRT) at 4 weeks or 6 months (Russo et al., 2016) and no significant difference in the California Verbal Learning Test-II (CVLT II) between patients who continued (persister) or discontinued (non-persister) nabiximols after the 4-week titration period (Carotenuto et al., 2020). An observational pilot study involving 20 patients reported significant benefit relative to baseline with nabiximols at 6 months and 12 months (both $p = 0.0001$) in group results of the California Verbal Learning Test (CVLT) but not in five other verbal memory assessments (Alessandria et al., 2020).

3.2.4. *Visual memory*

Neither of two real-world studies of nabiximols which used the Brief Visuospatial Memory Test – Revised (BVMT-R) to assess visual memory reported any significant change from baseline (Carotenuto et al., 2020; Alessandria et al., 2020).

3.2.5. *Attention*

A real-world study that used the Attentive Matrices (AM) test to assess impairment in the attention domain found no changes from baseline with nabiximols at 4 weeks or 6 months (Russo et al., 2016).

3.2.6. *Visuospatial processing*

No study specifically assessed aspects of visuospatial processing as a cognitive endpoint.

3.2.7. *Multiple domain screenings*

No significant differences between nabiximols and placebo were identified in a 6-week RCT in which the Short Orientation Memory and Concentration (SOMC) test was performed in patients with MS (Wade et al., 2004). A real-world study of nabiximols which undertook multiple domain screening using the Montreal Cognitive Assessment (MoCA) tool reported no differences from baseline at 4 weeks or 6 months (Russo

Table 2
Cognitive assessment outcomes in studies (any type) of nabiximols in spasticity due to MS ($n = 7$).

	RCTs			Non-interventional studies			
	Wade 2004	Aragona 2009	Vachová 2014	Russo 2016	Castelli 2019	Carotenuto 2020	Alessandria 2020
Study type, as described by authors	Parallel group, double-blind, placebo-controlled RCT	Double-blind, placebo-controlled, crossover RCT	Parallel group, double-blind, placebo-controlled RCT	Single-center, prospective, real-world follow-up study	Single-center, prospective, real-world follow-up study	Single-center, retrospective, real-world follow-up study	Prospective, single-blind, uncontrolled observational study
Primary study objectives	To assess the efficacy and tolerability of an oromucosal combined preparation of THC and CBD in the amelioration of multiple symptoms associated with MS	To explore the onset of psychopathological symptoms and cognitive deficits in cannabis-naive patients with MS treated with a cannabis plant extract (Sativex) for relieving their spasticity	The study was done as part of the risk management plan required by the European regulatory agencies, with the primary objective of evaluating whether Sativex may have long-term adverse effects on cognitive function or mood in patients with MS spasticity. The efficacy of long-term Sativex use on the severity of spasticity was also evaluated	To i) characterize the effects of 1- and 6-month Sativex administration in cannabis-naïve MS patients on their neurobehavioral function; ii) evaluate the drug tolerability and possible abuse phenomena induction; iii) study the effects of cannabis on QoL and motor functions, using a specific clinical and neuropsychological assessment	To investigate the effect of nabiximols on balance control in a cohort of patients with MS	To evaluate baseline predictors of long-term treatment discontinuation in a large cohort of patients in a real-world setting. To evaluate whether the extent of physical disability and cognitive impairment predict nabiximols persistence	To assess any variation on the same patient before and after Sativex administration up to one-year of observation period. A possible influence of cannabinoids on aspects related to mood and anxiety was also evaluated
Funding, as described by authors	Funded by GW Pharmaceuticals. GW Pharma Ltd contributed to the study design and was involved in data collection. Data handling and analysis were contracted by GW Pharma Ltd to an independent research organization	Sativex was kindly provided by GW Pharma Ltd, Salisbury, England. The grant was supported as the Project of University Research (ex-quota 60%) - year 2004 - by the University 'Sapienza' of Rome	GW Pharma Ltd, UK	NR	The author(s) received no financial support for the research, authorship and/or publication of this article	This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors	The study was supported by Almirall SpA. The study sponsor had no role in the study design; in the collection, analysis and interpretation of data; in the writing of the manuscript
Study location	UK (3 clinical centers)	Italy (single center)	Czech Republic (6 sites)	Italy (single center)	Italy (single center)	Italy (single center)	Italy (2 clinics)
Healthcare setting	Patients were recruited through outpatient clinics or general practitioners	MS outpatient clinic at 'Sapienza' University	NR	Single clinic	Single clinic, real-life setting	Single clinic, real-life setting	NR
Study timelines	May 2001 to July 2002	NR	NR	January and December 2014	NR	Nabiximols prescription between 01/09/2013 and 31/12/2017	Between May 2016 and May 2017
Population	MS, including patients with spasticity (90% in nabiximols group and 85% in placebo group)	MS spasticity	MS spasticity	MS spasticity	MS spasticity	MS spasticity	MS spasticity
Number of participants	160 Randomized = 160: - Nabiximols = 80 - Placebo = 80 Assessed at W6: - Nabiximols = 77 - Placebo = 77	17 Randomized = 17: - Nabiximols = 17 - Placebo = 17 (cross-over) Assessed: - Nabiximols = 17 - Placebo = 17	121 Randomized, safety analysis set: - Nabiximols = 62 - Placebo = 59 Per protocol analysis set at W48: - Nabiximols = 56 - Placebo = 58 Completed: - Nabiximols = 50 - Placebo = 48	61 Entered study = 61 Assessed = 40	22 Entered study = 22 Stayed on treatment after 12 months = 11	396 Entered 4-week titration phase = 396 Entered follow-up phase = 266 (persistent) Completed = 136 (persistent) Dropped out = 130 (non-persistent)	35 Enrolled = 35 Non-responder after 2 weeks initial treatment = 10 Fully evaluated = 20
Female, %	Nabiximols 59% Placebo 65%	Nabiximols 65% Placebo 65%	Nabiximols 63% Placebo 63%	NR	59%	58%	55%
Age, years, mean (SD); range	Nabiximols 51.0 (9.4); 27−74 Placebo 50.4 (9.3); 27−74	Nabiximols 49.8 (6.6) Placebo 49.8 (6.6)	Nabiximols 49.0 (9.0) Placebo 48.2 (10.4)	42 (8.9)	49.7 (8.3)	48.3 (9.1)	50.2 (11.4)

(*continued on next page*)

Table 2 (*continued*)

	RCTs			Non-interventional studies			
	Wade 2004	Aragona 2009	Vachová 2014	Russo 2016	Castelli 2019	Carotenuto 2020	Alessandria 2020
EDSS, mean (SD), range	NR	6.1 (0.3)	NR	Median (range): 7 (2−9)	Median (range): 5.0 (2.5–6.5)	5.5 (2.5–7.0)	Median (min-max): 6.0 (3.5–8.0)
Previous 'medicinal' cannabis, incl. dose	Nabiximols 37.5% Placebo 40.0%	No previous use of cannabis	Nabiximols 40% Placebo 25% (not specified)	NR No use of other cannabinoid-based medications (e.g. oral cannabinoid, smoked cannabis)	NR	NR	NR
Previous recreational cannabis, incl. dose	Nabiximols 16.3% Placebo 26.3%	No previous use of cannabis	See above	NR No use of other cannabinoid-based medications (e.g. oral cannabinoid, smoked cannabis)	NR	NR	NR
Assessment time point (s)	6 weeks	3 weeks	48 weeks	4 weeks 6 months	1 month 3 month 12 month	4 weeks NR, at some time-point between weeks 4 and 56	6 months 12 months
Processing speed	AMIPB: Nabiximols MD = 1.90 (n = 73); Placebo MD = 2.01 (n = 70); Diff. = -0.11 (95% CI -1.85 to 1.64), p = 0.904	PASAT: Nabiximols: mean (SD) = 43.0 (11.8); Placebo: mean (SD) = 42.4 (13.6), p = 0.79	PASAT (3s and 2s combined total score): Nabiximols: MD = 6.02; Placebo: MD = 7.49; Diff. = -1.47, (95% CI -6.41, NR), non-inferior	NR	NR	SDMT: 4 weeks: mean (SD): persistent [n = 266] 36.4 (11.5), non-persistent [n = 130] 36.4 (9.6), p = 0.97 >4 weeks: mean (SD): persistent [n = 136] 37.3 (11.5), non-persistent [n = 130] 35.3 (11.6), p = 0.26	PASAT-3: Change 6 months, median (min-max): 2.0 (-6.0–13.0), p = 0.314 Change 12 months, median (min-max): 3.0 (-3.0–16.0), p = 0.030 PASAT-2: Change 6 months, median (min-max): 3.0 (-7.0–16.0), p = 0.125 Change 12 months, median (min-max): −2.0 (-4.0–7.0), p = 0.719 SDMT: Change 6 months, median (min-max): 2.5 (-2.0–11.0), p < 0.001 Change 12 months, median (min-max): 2.0 (-5.0–11.0), p = 0.020
Executive function	NR	NR	NR	TMT A: Baseline: 79 (6) 4 weeks: 74 (7) 6 months: 72 (6) TMT B: Baseline: 181 (18) 4 weeks: 168 (19) 6 months: 166 (19) TMT B-A: Baseline: 115 (16) 4 weeks: 94 (13) 6 months: 93 (14)	SCWT: 1 month: reported as a graphic 3 months: reported as a graphic 12 months: reported as a graphic	NR	NR
Verbal memory	NR	NR	NR	BSRT: 4 weeks: 9 (1) 6 months: 9 (1)	NR	CVLT II: 4 weeks, mean (SD): persistent [n = 266] 34.6 (11), non-persistent [n = 130] 34.5 (10.2), p = 0.92 >4 weeks, mean (SD): persistent [n = 136] 34 (10.5), non-persistent [n = 130] 35.5 (11.8), p = 0.40	CVLT-2: Change 6 months, median (min-max): 5.7 (-7.0–20.0), p = 0.0001 Change 12 months, median (min-max): 7.0 (-2.0–20.0), p < 0.0001 FCSRT – IFR (corrected): Change 6 months, median (min-max): 0.9 (-4.0–7.0), p = 0.235 Change 12 months, median (min-max): 1.0 (-6.0–5.0), p = 0.175 FCSRT – ITR: Change 6 months, median (min-max):

(*continued on next page*)

Table 2 (*continued*)

	RCTs Wade 2004	Aragona 2009	Vachová 2014	Non-interventional studies Russo 2016	Castelli 2019	Carotenuto 2020	Alessandria 2020
							0.0 (-1.0–2.0), $p = 0.313$ Change 12 months, median (min-max): 0.0 (-1.0–2.0), $p = 0.344$ FCSRT – DFR (corrected): Change 6 months, median (min-max): 0.0 (-3.0–2.0), $p = 0.903$ Change 12 months, median (min-max): 0.0 (-2.0–2.0), $p = 0.649$ FCSRT – DTR: Change 6 months, median (min-max): 0.0 (-1.0–1.0), $p = 0.000$ Change 12 months, median (min-max): 0.0 (0.0 to 0.0), p = n.a. ISC: Change 6 months, median (min-max): 0.0 (-0.2 to 0.1), $p = 0.625$ Change 12 months, median (min-max): 0.0 (-0.1 to 0.1), $p = 0.750$
Visual memory	NR	NR	NR	NR	NR	BVMT-R: 4 weeks, mean (SD): persistent [$n = 266$] 38.8 (10.6), non-persistent [$n = 130$] 37.9 (8.9), $p = 0.53$ >4 weeks, mean (SD): persistent [$n = 136$] 38.9 (10.3), non-persistent [$n = 130$] 38.7 (11.1), $p = 0.90$	BVMT-R: Change 6 months, median (min-max): −2.0 (-10.0–18.0), $p = 0.508$ Change 12 months, median (min-max): −1.0 (-19.0–22.0), $p = 0.228$
Attention	NR	NR	NR	AM: Baseline: 42 (1) 4 weeks: 43 (1) 6 months: 43 (1)	NR	NR	NR
Visuospatial processing	NR	NR	NR	NR	NR	NR	NR
Multiple domain screenings	From ct.gov (*) SOMC: Nabiximols MD = -1.0 ($n = 78$), SD = 5.02, Placebo MD = 0.0, SD = 3.20 ($n = 76$), Diff. = NR (95% CI NR); p = NR	NR	NR	MoCA: 4 weeks: 28 (1) 6 months: 28 (1)	NR	BICAMS impairment: No, N (%): 4 weeks: persistent [$n = 266$] 40 (24.5), non-persistent [$n = 130$] 18 (21.2), $p = 0.55$ > 4 weeks: persistent [$n = 136$] 25 (26.9), non-persistent [$n = 130$] 15 (21.4), $p = 0.42$ Yes, N (%) 4 weeks: persistent [$n = 266$] 123 (75.5), non-persistent [$n = 130$] 67 (78.8) >4 weeks: persistent [$n = 266$] 68 (73.1), non/persistent [$n = 130$] 55 (78.6)	NR
Conclusion, as reported by authors	There were no significant adverse effects on cognition or mood and intoxication was generally mild.	Cannabinoid treatment did not induce psychopathology and did not impair cognition in cannabis-naive patients	Long-term treatment with Sativex was not associated with cognitive decline or significant changes in	Our findings show that Sativex treatment does not significantly affect the cognitive and neurobehavioral domains at a	Our findings suggest that nabiximols had a detrimental effect	Higher physical and cognitive disability predicted nabiximols treatment discontinuation over 2 years	These results are encouraging in supporting possible long-term benefits of Sativex on cognition and a

(*continued on next page*)

Table 2 (*continued*)

RCTs Wade 2004	Aragona 2009	Vachová 2014	Non-interventional studies Russo 2016	Castelli 2019	Carotenuto 2020	Alessandria 2020
	with MS…. (…) At dosages higher than those used in therapeutic settings, interpersonal sensitivity, aggressiveness, and paranoid (or paranoia-like) features might arise (…)	mood in this prone population sample. Sativex was efficacious and well tolerated across the study period and no new safety concerns were identified.	moderate dosage. However, the study supports the relevance of an extensive neuropsychological evaluation in patients who are selected for the drug administration, in an attempt to early detect the uncommon but important neurobehavioral side effects.	on postural control, especially in multi-tasking conditions.	in MS patients suffering from spasticity. Nabiximols should be started earlier to decrease the likelihood of treatment discontinuation over time.	wider role than symptom alleviator. Further studies on larger groups of patients would be necessary in order to test this intriguing possibility.

AM, Attentive Matrices; AMIPB, Adult Memory and Information Processing Battery; BICAMS, Brief International Cognitive Assessment for Multiple Sclerosis; BSRT, Babcock Story Recall Test; BVMT-R, Brief Visuospatial Memory Test-Revised; CBD, cannabidiol; CBM, cannabis-based medicine; CI, confidence interval; ct.gov, www.clinicaltrials.gov; CVLT, California Verbal Learning Test; CVLT II, California Verbal Learning Test-II; DFR, Delayed Free Recall; Diff., difference between groups; DTR, Delayed Total Recall; EDSS, Expanded Disability Status Scale; FCSRT, Free and Cued Selective Reminding Test; IFR, Immediate Free Recall; ISC, Index of Sensitivity of Cueing; ITR, Immediate Total Recall; MD, mean difference to baseline; MoCA, Montreal Cognitive Assessment; MS, multiple sclerosis; NPS, Neuropathic Pain Scale; NR, not reported; PASAT, Paced Auditory Serial Addition Test; PASAT 2s, Paced Auditory Serial Addition Test 2 seconds; PASAT 3s, Paced Auditory Serial Addition Test 3 seconds; QoL, quality of life; RCT, randomized controlled trial; SCWT, Stroop Color and Word Test; SD, standard deviation; SDMT, Symbol Digit Modalities Test; SOMC, Short Orientation Memory and Concentration Test; THC, tetrahydrocannabinol; TMT A, Trail Making Test Part A; TMT B, Trail Making Test Part B; W, week.
(*) Additional information was extracted from ct.gov.

et al., 2016). A retrospective real-world study which used the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) to assess cognitive function in persisters ($n = 136$) and non-persisters ($n = 130$) of nabiximols treatment reported neither deterioration nor improvement relative to baseline in integrative BICAMS impairment in either group at 4 weeks, i.e., end of titration phase, or at a non-specified timepoint between 4 and 56 weeks (mean follow-up time was 43 ± 13.4 months). BICAMS impairment at baseline was highly predictive for treatment discontinuation at follow-up (HR 21.87; 95% CI 2.55, 188.14, $p = 0.005$) (Carotenuto et al., 2020).

3.3. Cognitive AEs in RCTs of nabiximols versus placebo in MS

Thirteen double-blind RCTs were identified of nabiximols versus placebo in patients with MS (Wade et al., 2004; Aragona et al., 2009; Vachová et al., 2014; Rog et al., 2005; Collin et al., 2007; Collin et al., 2010; Kavia et al., 2010; Notcutt et al., 2012; ClinicalTrials.gov 2012; Langford et al., 2013; Novotna et al., 2011; Leocani et al., 2015; Markovà et al., 2019). Eight RCTs were conducted in patients with spasticity due to MS (Aragona et al., 2009; Wade et al., 2004; Collin et al., 2007; Collin et al., 2010; Kavia et al., 2010; Novotna et al., 2011; Leocani et al., 2015; Markovà et al., 2019), three RCTs were focused on central (Rog et al., 2005), chronic refractory (ClinicalTrials.gov 2012), or central neuropathic (Langford et al., 2013) pain in MS patients, one RCT evaluated multiple symptoms associated with MS (Wade et al., 2004), and one RCT was dedicated to detrusor overactivity in MS (Kavia et al., 2010). Across studies, a total of 964 patients (range: 15 to 167) were treated with nabiximols and 904 patients (range: 17 to 172) were treated with placebo. Treatment duration ranged from 3 to 48 weeks and maximum nabiximols dosage ranged from 12 to 48 sprays/day. Use of nabiximols not in accordance with the European label ('not in-label') was recorded for nine studies (Wade et al., 2004; Aragona et al., 2009; Rog et al., 2005; Collin et al., 2007; Collin et al., 2010; Kavia et al., 2010; Notcutt et al., 2012; ClinicalTrials.gov 2012; Langford et al., 2013), and use of nabiximols in accordance with the European label ('in-label') was recorded for four studies (Vachová et al., 2014; Novotna et al., 2011; Leocani et al., 2015; Markovà et al., 2019). Main reasons for not in-label use were exceeding the current maximum dosage recommendations of 12 sprays/day (Wade et al., 2004; Aragona et al., 2009; Rog et al., 2005; Collin et al., 2007; Collin et al., 2010; Kavia et al., 2010; Notcutt et al., 2012; ClinicalTrials.gov 2012), and/or administering nabiximols not for the primary purpose of treating MS spasticity (Wade et al., 2004; Rog et al., 2005; Kavia et al., 2010; ClinicalTrials.gov 2012; Langford et al., 2013).

Assessment with the RoB 2 tool revealed moderate overall risk of bias for all RCTs, mainly due to uncertainties in the operationalization of cognitive AE reporting (Fig. 2). In all studies, cognitive AEs were reported by investigators without application of specific cognitive instruments for qualitative and quantitative assessment. In one study, AEs with an incidence of ≤4% were not reported (Wade et al., 2004).

Cognitive AEs with nabiximols in MS were reported in six of the 13 included RCTs (Table 4) (Wade et al., 2004; Vachová et al., 2014; Rog et al., 2005; Collin et al., 2007; Langford et al., 2013; Markovà et al., 2019). Of 32 cognitive AEs reported in nabiximols arms, the most common was 'disturbance in attention' (19 events, 59%). More than half of all cognitive AEs (17 events, 53%) were reported in one study which investigated nabiximols for relief of central neuropathic pain in patients with MS (Langford et al., 2013) The majority of cognitive AEs (30 events, 93.8%) were reported in studies of not in-label use of nabiximols.

Meta-analysis was possible for the cognitive AEs of memory impairment, psychomotor skills impaired, and disturbance in attention. Compared with placebo, nabiximols use was associated with a greater likelihood of these cognitive AEs, with an OR of 5.02 (95% CI 0.85, 29.62) for memory impairment (Fig. 3A) (Vachová et al., 2014; Langford et al., 2013), 6.41 (95% CI 0.74, 55.39) for psychomotor skills impaired (Fig. 3B) (Langford et al., 2013; Markovà et al., 2019), and

Table 3
Evidence quality using the Cochrane grading of recommendations assessment, development, and evaluation (GRADE) tool.

Patient or population: Spasticity due to MS Setting: Hospital or ambulant Intervention: Nabiximols Comparison: Any comparator Outcomes	No. of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects Risk with any comparator	 Risk difference with nabiximols
Incidence of AE 'Cognitive Disorder', 'Memory impairment', 'Psychomotor skills impaired', 'Disturbance in attention' (Cognitive AEs) Assessed with: Preferred Term (PT), System − Organ − Class (SOC) Follow-up: range 4 weeks to 48 weeks	2040 (13 RCTs)	⊕⊕○○ Low[a,b,c]	13 RCTs were identified. The outcome was suitable for meta-analysis.		
Cognitive functions as measured with specific cognitive instruments (Cognitive functions) Assessed with: Specific cognitive instruments Follow-up: range 4 weeks to 50 weeks	312 (3 RCTs)	⊕○○○ Very low[d]	Three RCTs with specific cognitive assessments were identified and qualitatively assessed. Meta-analysis was not possible due to heterogeneous cognitive assessment instruments and outcomes.		
Cognitive functions as measured with specific cognitive instruments (Cognitive functions) Assessed with: Specific cognitive instruments Follow-up: range 6 months to 65 months	514 (4 observational studies)	⊕○○○ Very low[e,f]	Four non-RCTs with specific cognitive assessments, three prospective and one retrospective, were identified and narratively assessed. Meta-analysis was not possible due to heterogeneous cognitive assessment instruments and outcomes.		

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
GRADE Working Group grades of evidence, High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.

[a] The incidence rates of cognitive AEs vary from study to study. The subgroup analysis suggests, however, effect modification through use of nabiximols in higher than approved daily dosage.
[b] Meta-analysis of outcome AE 'Cognitive disorder' was not possible because it was not reported in any of the 13 studies.
[c] The cognitive AEs were apparently diagnosed without using specific cognitive instruments. There is a risk of confounding due to psychological or psychiatric AEs, which can influence or mimic cognitive symptoms.
[d] All three studies suggested no effect of nabiximols treatment of spasticity due to MS on cognitive functions.
[e] Four non-randomized studies, three prospective and one retrospective.
[f] One study suggested a positive effect of nabiximols on cognitive function, one study speculated prevention effect of treatment with nabiximols, one study suggested no effect of nabiximols treatment of spasticity due to MS on cognitive functions, and one study suggested some cognitive decrease but only during dual-test with postural challenge.

AE, adverse event; CI, confidence interval; MS, multiple sclerosis; RCT, randomized controlled trial.

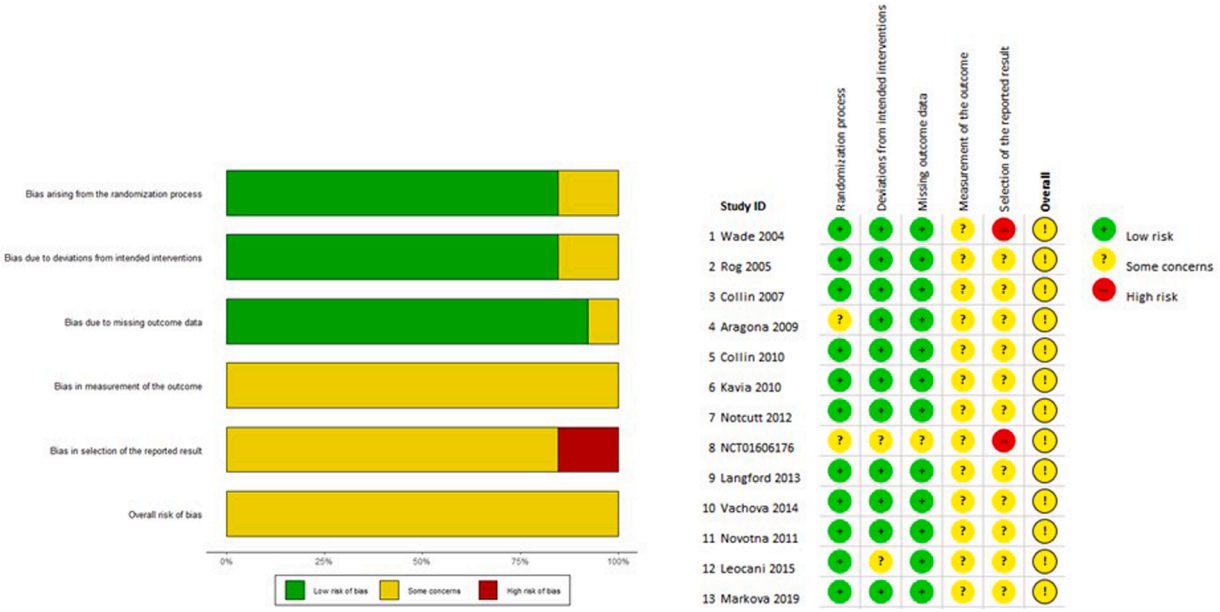

Fig. 2. Risk of bias (RoB 2) of RCTs included in the meta-analysis of cognitive adverse events. RCTs, randomized controlled trials; RoB 2, Risk of Bias 2 tool.

7.06 (95% CI 1.86, 26.77) for disturbance in attention (Fig. 3C) (Wade et al., 2004; Rog et al., 2005; Collin et al., 2007; Langford et al., 2013).

A subgroup-analysis of 'in-label' versus 'not in-label' use showed that cognitive AEs occurred more frequently with nabiximols compared with placebo only when nabiximols was not used according to its approved label (Fig. 4).

Psychiatric AEs reported in RCTs of nabiximols versus placebo are itemized in Supplementary File 3.

Table 4
Characteristics of double-blind placebo-controlled randomized studies of nabiximols included in the meta-analysis ($n = 13$) and cognitive adverse events reported per study.

	Not in-label use ($n = 9$)*									In-label use ($n = 4$)			
	Wade 2004	Rog 2005	Collin 2007	Aragona 2009	Collin 2010	Kavia 2010	Notcutt 2012	NCT01606176	Langford 2013	Vachová 2014	Novotna 2011	Leocani 2015	Markova 2019
NCT number (ct.gov)	NCT01610700	NCT01604265	NCT00711646	NA	NCT01599234	NCT00678795	NCT00702468	NCT01606176	NCT00391079	NCT01964547	NCT00681538	NCT01538225	NA
Indication	MS	Central pain in MS	Spasticity due to MS	Spasticity due to MS	Spasticity due to MS	Detrusor overactivity in MS	Spasticity due to MS	Chronic refractory pain due to MS or other defects of neurological function	Central neuropathic pain in patients with MS	Spasticity due to MS	Spasticity due to MS	Spasticity due to MS	Spasticity due to MS
Nabiximols, n	80	34	124	17	167	67	18	36	167	62	124	15	53
Placebo, n	80	32	65	17	170	68	18	34	172	59	117	19	53
Treatment duration vs. placebo, weeks	10	4	6	3	14	8	4	4	14	48	12	4	12
Maximum daily dosage, sprays	44	48	48	>12	24	48	48	48	12	12	12	12	12
Cognitive disorder													
Nabiximols	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Placebo	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR**	NR	NR	NR
Memory impairment													
Nabiximols	NR	NR	NR	NR	NR	NR	NR	NR	6	1	NR	NR	NR
Placebo	NR	NR	NR	NR	NR	NR	NR	NR	1	0	NR	NR	NR
Psychomotor skills impaired													
Nabiximols	NR	NR	NR	NR	NR	NR	NR	NR	5	NR	NR	NR	1
Placebo	NR	NR	NR	NR	NR	NR	NR	NR	0	NR	NR	NR	0
Disturbance in attention													
Nabiximols	7	2	4	NR	NR	NR	NR	NR	6	NR	NR	NR	NR
Placebo	0	0	0	NR	NR	NR	NR	NR	1	NR	NR	NR	NR

NR, none reported; (*) Not in-label use is defined as dosage >12 sprays/day and/or nabiximols administered not for treatment of spasticity due to MS [Electronic Medicines Compendium 2021]; (**) According to the information reported on www.clinicaltrials.gov there was one case of 'cognitive disorder' in the placebo group [https://clinicaltrials.gov/ct2/show/study/NCT01964547]. However, this case is not mentioned in the peer-reviewed publication [Vachová et al., 2014].

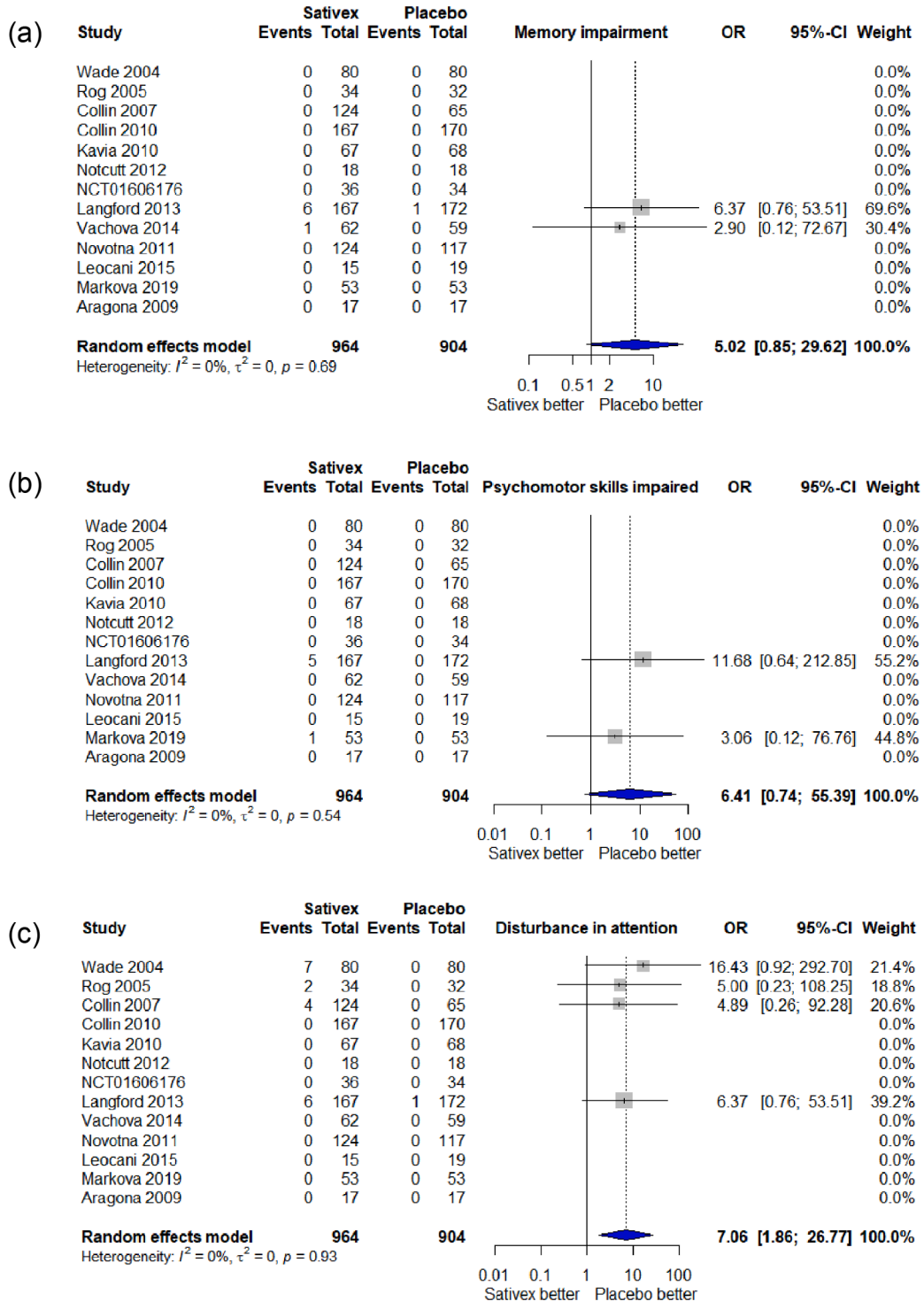

Fig. 3. Meta-analysis of cognitive adverse events.

4. Discussion

This systematic review assessed available evidence regarding the impact of nabiximols treatment on cognitive function in patients with MS.

There is no compelling supportive evidence to suggest that nabiximols causes cognitive impairment in this prone population as assessed in studies which used a wide range of specific cognitive instruments. None of the seven RCTs or observational studies assessing cognition as an endpoint for up to 12 months reported any association between nabiximols treatment and cognitive decline across multiple cognitive domains (Wade et al., 2004; Aragona et al., 2009; Vachová et al., 2014; Russo et al., 2016; Castelli et al., 2019; Carotenuto et al., 2020; Alessandria et al., 2020). Importantly, a 12-month, placebo-controlled RCT (Vachová et al., 2014) conducted as part of the European Medicine Agency's risk management plan following initial authorization of nabiximols in 2010 confirmed the adequacy of current European nabiximols prescribing information. A 12-month pilot study from Italy investigating cognitive effects of nabiximols in MS spasticity concluded that results were encouraging in terms of supporting the possible

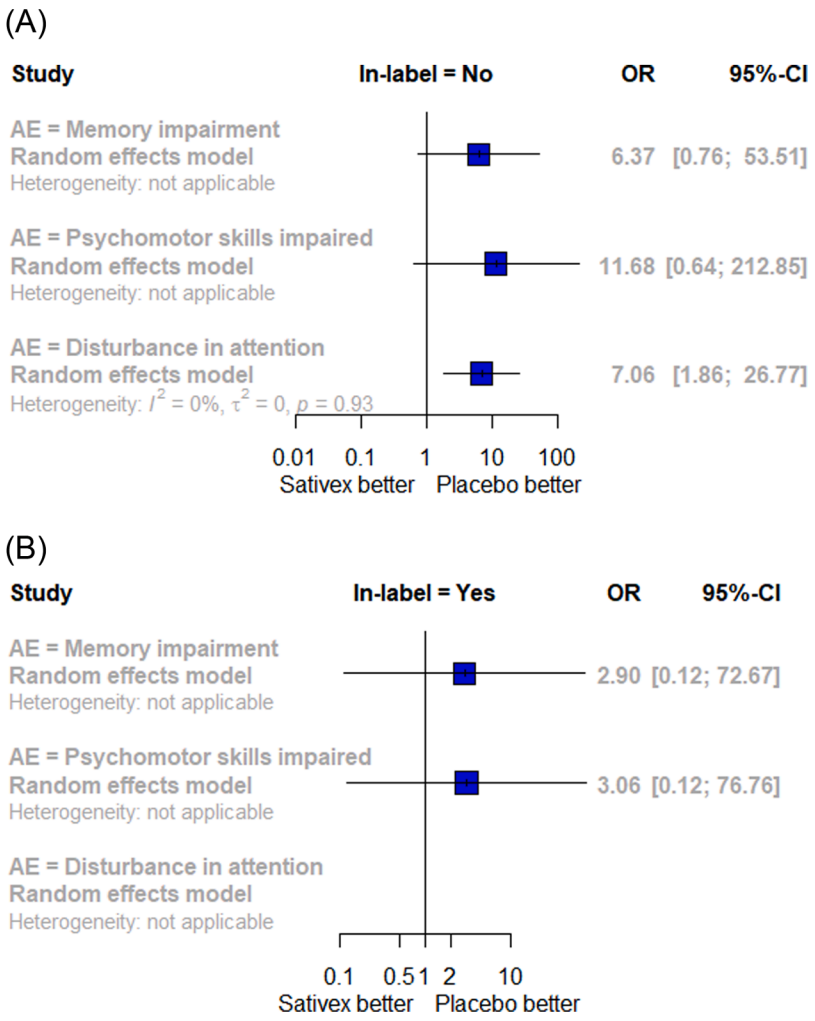

Fig. 4. Subgroup analysis: cognitive adverse events for not in-label (top panel) versus in-label (bottom panel) use of nabiximols.

long-term benefits of nabiximols on cognition based on significant improvement observed in some measures of processing speed and auditory verbal memory (Alessandria et al., 2020). However, the study was limited by its small sample size and is likely to have incorporated practice effects due to the higher frequency of cognitive testing across the 12-month follow-up. A recent analysis of pooled data for 362 MS patients from two RCTs (Vachová et al., 2014; Novotna et al., 2011) concluded that nabiximols does not adversely affect working memory and cognitive processing speed in MS patients over a 48-week period compared with placebo (DeLuca et al., 2021).

Meta-analysis showed that cognitive AEs are rare in cases of in-label use of nabiximols for MS spasticity. In fact, 30 (93.8%) of the 32 nabiximols-related cognitive AEs reported in six of 13 eligible placebo-controlled RCTs occurred only when maximum dosages of 44−48 sprays/day were allowed and in the absence of the titration regimen currently specified in the European approved label (Wade et al., 2004; Rog et al., 2005; Collin et al., 2007) or when label-conform dosing of nabiximols was used primarily to treat central neuropathic pain (not specifically MS spasticity) in MS patients (Langford et al., 2013). It is noteworthy that most studies using higher doses of nabiximols were conducted during its clinical development and prior to its European approval; these studies ultimately informed the current approved maximum dosage of 12 sprays per day (Electronic Medicines Compendium, 2021).

The rarity of cognitive AEs with nabiximols during in-label use is not surprising given that their potential is likely to depend on the composition, dosage and route of administration of cannabinoid products. Lucas et al. (2018) noted that the effects of herbal cannabis are proportionate to the plasma THC concentration, and that the rapid increase in plasma THC concentration after inhaling cannabis increases the risk of adverse effects (Lucas et al., 2018). Plasma THC concentrations can vary considerably depending on product source: nonmedical-grade cannabis products in particular contain unknown quantities of THC and CBD (Lucas et al., 2018). Nabiximols is a standardized formulation containing a balanced concentration of THC and CBD (Electronic Medicines Compendium 2021). Oromucosal delivery facilitates rapid absorption while producing plasma THC concentrations much lower than that of inhaled cannabis (Lucas et al., 2018), thus minimizing the likelihood of THC-associated adverse effects. A German Pain e-Registry analysis involving patients with severe refractory neuropathic pain found that incidences of nervous system disorders (9.5% vs. 19.9%; $p < 0.001$) and psychiatric disorders (4.2% vs. 14.8%; $p < 0.001$) were significantly lower with add-on nabiximols versus add-on dronabinol (synthetic THC) therapy, emphasizing the importance of including CBD in the formulation (Ueberall et al., 2022).

The low incidence of nabiximols-related cognitive AEs as reported across the 13 RCTs included in our analysis aligns with the results of a comprehensive safety review of 15 RCTs and associated open-label studies of nabiximols conducted and published (including on the clinicaltrials.gov website) over the past 15 years (Prieto González and Vila Silván, 2021). Although cognitive impairments can occur in patients receiving nabiximols, evidence suggests that they are uncommon, which

is important and reassuring for MS patients in terms of maintaining their autonomy and ability to perform daily life activities. In this context, a pilot study without a control arm that assessed driving ability in patients receiving nabiximols for MS spasticity ($n = 33$) identified no differences from baseline in a battery of validated computerized tests after 4 to 6 weeks of treatment (Freidel et al., 2015).

Cognitive impairment is a heterogenous comorbidity of MS due to individual variation in the extent and location of CNS damage (Rahn et al., 2012). Assessment of cognition presents methodological challenges since cognition is difficult to measure due to its multiple facets and is not conducive to accurate self-reporting (Gingerich and Yeates, 2019). Moreover, cognitive assessment tools vary considerably across countries and treatment centers. A systematic review aimed at identifying cognitive measures used in MS research reported that 5665 measures had been employed across 1526 included studies, of which some were potentially inappropriate because they measured irrelevant domains or were insufficiently sensitive (Elwick et al., 2021).

In 2012, the BICAMS screening instrument was introduced and recommended by leading experts in the field (Langdon et al., 2012). The BICAMS battery explores three different cognitive domains frequently affected by MS. The Symbol Digit Modalities Test (SDMT) (Smith, 1982) is generally used to assess information processing speed and working memory. The California Verbal Learning Test (CVLT-II) (Delis et al., 2000) is used to evaluate verbal short-term memory and learning. The Brief Visuospatial Memory Test - Revised (BVMT-R) (Benedict, 1997) is used to assess visuospatial short-term memory and learning. Importantly, BICAMS takes only 15 minutes to complete in clinical practice, and requires no specialist equipment or specialist expertise in cognitive assessment (Langdon et al., 2012; Penner et al., 2021). BICAMS is currently validated across more than 10 languages and offers a feasible and cost-effective means of assessing cognition in MS patients in daily practice (Corfield and Langdon, 2018). Investigators and clinicians may appreciate application of the BICAMS instrument in future nabiximols studies in order to allow for direct comparison across centers.

4.1. Limitations

This review has limitations. The number of studies using psychometric cognitive assessments was limited and GRADE-assessed quality of evidence concerning cognitive outcomes and AEs was low. Some studies were not controlled. Cognitive assessment instruments were heterogenous and may have been subject to measurement limitation, i.e., not sufficiently sensitive to measure a change in cognitive burden. There is potential for bias in the reporting of cognitive AEs in nabiximols RCTs since they were not validated using specific psychometric instruments; however, it must be noted that investigators generally have to rely on subjective patient complaints regarding cognitive deficits or assess cognition using neuropsychological tests.

Psychiatric symptoms are indirectly interconnected with cognitive function. In clinical practice, psychiatric symptoms (e.g., somnolence, euphoria, depression) may influence or confound the results of cognitive tests and reports of AEs (Strober et al., 2016). Our initial plans to perform additional meta-analysis for psychiatric AEs had to be abandoned once it became apparent that assessing the confounding effect of psychiatric AEs on cognitive tests would not be possible without access to patient-level data. For the same reason, it was not possible to assess the confounding effects of age, co-morbidities, or concomitant antispasticity (or other) medication on cognitive tests.

5. Conclusion

To our knowledge, this is the first systematic review to examine the potential effects of a single cannabinoid product (nabiximols) on cognitive function in patients with MS, providing a degree of specificity in terms of conclusions. Within the limitations of the review, we can assume from the evidence that no detrimental effects on cognition are to be expected in patients with MS spasticity treated with nabiximols for up to 12 months, and that cognitive AEs are rare and apparent only when nabiximols is not used according to its approved label. Well-designed and sufficiently powered clinical studies using standardized cognitive assessment instruments validated in MS, preferably the multiple domain BICAMS screening battery, would be highly welcome to assess with greater certainty the potential for direct cognitive effects of nabiximols treatment in MS patients.

Sources of support

None

Ethical considerations

This article is a systematic review and did not require approval from an institutional review board.

Data sharing policy

The data that support the findings of the review are available as supplementary files in the online version or from the corresponding author upon reasonable request.

Supplementary Files

Supplementary material associated with the article can be found in the online version at doi: xxxx.

Supplementary File 1. Systematic literature search details.

Supplementary File 2. Cognitive function outcomes using validated psychometric instruments reported in clinical studies (any type) of nabiximols.

Supplementary File 3. Cognitive adverse events reported in randomized controlled trials of nabiximols versus placebo.

CRediT authorship contribution statement

Igor Dykukha: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Ute Essner:** Conceptualization, Data curation, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Herbert Schreiber:** Conceptualization, Writing – original draft, Writing – review & editing. **Lina Marie Raithel:** Writing – review & editing. **Iris-Katharina Penner:** Conceptualization, Formal analysis, Methodology, Validation, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

Igor Dykukha is an employee of Almirall Hermal GmbH and serves as medical advisor. Ute Essner has received honoraria for consultancy services from Almirall Hermal GmbH and Granzer Regulatory Consulting & Service. Herbert Schreiber has received honoraria and personal compensation for serving as a speaker at scientific meetings and member of advisory boards from Almirall, Alnylam, Bayer Pharma, Biogen, Merck, Novartis, Roche and Teva. He has received research grants from Bayer, Biogen, Novartis and Teva. Lina Marie Raithel has nothing to disclose. Iris-Katharina Penner has received honoraria for speaking at scientific meetings, serving at scientific advisory boards and consulting activities from Adamas Pharma, Almirall, Bayer Pharma, Biogen, BMS, Celgene, Desitin, Sanofi-Genzyme, Janssen, Merck, Novartis, Roche, and Teva. She has received research support from the German MS Society, Celgene, Novartis, Roche, and Teva. Almirall is a partner of GW Pharmaceuticals (developer of Sativex) in Europe.

Role of funding sources

The authors received no financial support for the research, authorship and/or publication of this article.

Acknowledgments

Medical writing assistance was provided by Kerry Dechant, ISMPP CMPP™ on behalf of Content Ed Net (Munich, Germany) with funding from Almirall Hermal GmbH (Reinbek, Germany).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2022.104173.

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