Il punto sulle terapie sintomatiche: spasticità e dolore

M. Dotta

A.S.L. CN2 Alba-Bra

Discussant

C. Solaro

PAIN® 154 (2013) 632–642

PAIN®

www.elsevier.com/locate/pain

Comprehensive review

Prevalence and natural history of pain in adults with multiple sclerosis: Systematic review and meta-analysis

Peter L. Foley [a,b,*], Hanna M. Vesterinen [a], Barry J. Laird [b,c], Emily S. Sena [a,d], Lesley A. Colvin [e], Siddharthan Chandran [a], Malcolm R. MacLeod [a], Marie T. Fallon [b]

[a] Division of Clinical Neurosciences, University of Edinburgh, Edinburgh, UK
[b] Department of Palliative Medicine, Edinburgh Cancer Research Centre, University of Edinburgh, Edinburgh, UK
[c] European Palliative Care Research Centre (PRC), Norwegian University of Science and Technology, Trondheim, Norway
[d] The Florey Institute of Neuroscience and Mental Health, Melbourne Brain Centre, University of Melbourne, Heidelberg, Australia
[e] Department of Anaesthesia and Pain Medicine, University of Edinburgh, Edinburgh, UK

- Overall pain prevalence 62.8%

spasticity symptoms 60%

Studio NARCOMS 2004 18727 Pz;

84% almeno un sintomo di spasticità

30% moderato-severo.

38% in terapia

Rizzo et al. Mult Scler 2004;10: 589–595

The prevalence of pain in multiple sclerosis

A multicenter cross-sectional study

C. Solaro, MD; G. Brichetto, MD; M.P. Amato, MD; E. Cocco, MD; B. Colombo, MD; G. D'Aleo, MD; C. Gasperini, MD; A. Ghezzi, MD; V. Martinelli, MD; C. Milanese, MD; F. Patti, MD; M. Trojano, MD; E. Verdun, MD; G.L. Mancardi, MD; and the PaIMS Study Group*

Abstract—In a multicenter cross-sectional study, the authors assessed pain in patients with multiple sclerosis (MS) using a symptom-oriented approach. Out of 2,077 questionnaires, we used 1,672 for data analysis. Pain and frequencies included trigeminal neuralgia 2%, Lhermitte's sign 9%, dysesthetic pain 18.1%, back pain 16.4%, and painful tonic spasms 11%. Comparison between different groups showed significant differences for age, Expanded Disability Status Scale, disease duration, and disease course, but not for sex. This study underlines the relevance of pain in the clinical history of MS.

NEUROLOGY 2004;63:919–921

then contradicted in a subsequent study.[5] The current study has shown a correlation between pain and age, EDSS, disease duration, disease course, but not sex. Moreover, this correlation was present for both typical neurogenic pain, such as dysesthetic pain and trigeminal neuralgia, and for typical somatic pain, including back pain and painful tonic spasms. It is possible that the correlation with disease severity could be due, in dysesthetic pain and painful tonic spasms, to spinal involvement and, in back pain, to abnormal posture and gait impairment.

Pain 137 (2008) 96–111

PAIN

www.elsevier.com/locate/pain

Pain associated with multiple sclerosis: Systematic review and proposed classification

Alec B. O'Connor [a], Steven R. Schwid [b], David N. Herrmann [b], John D. Markman [c], Robert H. Dworkin [b,d,*]

[a] *Department of Medicine, University of Rochester School of Medicine and Dentistry, 601 Elmwood Avenue, Rochester, NY 14642, USA*
[b] *Department of Neurology, University of Rochester School of Medicine and Dentistry, 601 Elmwood Avenue, Rochester, NY 14642, USA*
[c] *Department of Neurosurgery, University of Rochester School of Medicine and Dentistry, 601 Elmwood Avenue, Rochester, NY 14642, USA*
[d] *Department of Anesthesiology, University of Rochester School of Medicine and Dentistry, 601 Elmwood Avenue, Rochester, NY 14642, USA*

- **Dolore neuropatico centrale**

continuo

Dolore delle estremità “disestesico”

accessuale

Nevralgia trigeminale

Segno di Lhermitte

- **Dolore muscoloscheletrico**

Spasmi tonici dolorosi

Secondario a spasticità

Secondario a posture anomale ed ad altre complicanze

- **Cefalea**

PAIN® 154 (2013) 632–642

PAIN®

www.elsevier.com/locate/pain

Comprehensive review

Prevalence and natural history of pain in adults with multiple sclerosis: Systematic review and meta-analysis

Peter L. Foley [a,b,*], Hanna M. Vesterinen [a], Barry J. Laird [b,c], Emily S. Sena [a,d], Lesley A. Colvin [e], Siddharthan Chandran [a], Malcolm R. MacLeod [a], Marie T. Fallon [b]

[a] Division of Clinical Neurosciences, University of Edinburgh, Edinburgh, UK
[b] Department of Palliative Medicine, Edinburgh Cancer Research Centre, University of Edinburgh, Edinburgh, UK
[c] European Palliative Care Research Centre (PRC), Norwegian University of Science and Technology, Trondheim, Norway
[d] The Florey Institute of Neuroscience and Mental Health, Melbourne Brain Centre, University of Melbourne, Heidelberg, Australia
[e] Department of Anaesthesia and Pain Medicine, University of Edinburgh, Edinburgh, UK

- Cefalea 50% (ultimo mese)
- Dolore neuropatico delle estremità 26.6% (18%)
- Lombalgie 20% (16%)
- Spasmi dolorosi 15%(11%)
- Segno di Lhermitte 16.6% (9%)
- Nevralgia trigeminale 3.8% (2%)

Drugs 2010; 70 (10): 1245-1254
0012-6667/10/0010-1245/$55.55/0

Pharmacological Management of Pain in Patients with Multiple Sclerosis

Claudio Solaro[1] and *Michele Messmer Uccelli*[2]

1 Department of Neurology, ASL 3 Genovese, Genoa, Italy
2 Department of Research, Italian Multiple Sclerosis Society, Genoa, Italy

Table I. Studies of medications for central neuropathic pain in multiple sclerosis

Study (year)	Design	Medication	No. of patients	Mean dose	Efficacy	No. of patients with AE
Cianchetti et al.[14] (1999)[a]	Open-label	LMT	15	400 mg/day	2/15 complete; 6/15 partial	0
Breuer et al.[15] (2007)	Double-blind, crossover	LMT	12	400 mg/day	No difference vs placebo	1
Houtchens et al.[16] (1997)	Open-label	GBP	25	600 mg/day	15/22 complete or partial	11/22 (5 withdrawals)
Rossi et al.[17] (2009)	Single-blind	LEV	12 vs 8 placebo	3000 mg/day	Significant difference	8/12 (1 withdrawal)
Solaro et al.[18] (2009)	Open-label	PGB	16	154 mg/day	9/16 complete	(3 withdrawals)
Svendsen et al.[19] (2004)	Crossover	CNB	24	10 mg/day	Significantly lower pain during active treatment	23/24 (0 withdrawals)
Rog et al.[20] (2005)	Double-blind	CNB	34 vs 32 placebo	9.6 spray daily[b]	Significant difference active treatment vs placebo	30/34 (2 withdrawals)

a Previous therapy maintained.

b Each spray delivered 2.7 mg of Δ9-tethrahydrocannabinol and 2.5 mg of cannabidiol.

AE = adverse event; **CNB** = cannabinoid; **GBP** = gabapentin; **LEV** = levetiracetam; **LMT** = lamotrigine; **PGB** = pregabalin.

Treatment

All neuropathic pain (except trigeminal neuralgia)

1.1.8 Offer a choice of amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment for neuropathic pain (except trigeminal neuralgia)[3].

1.1.9 If the initial treatment is not effective or is not tolerated, offer one of the remaining 3 drugs, and consider switching again if the second and third drugs tried are also not effective or not tolerated.

1.1.10 Consider tramadol only if acute rescue therapy is needed (see recommendation 1.1.12 about long-term use).

1.1.11 Consider capsaicin cream[4] for people with localised neuropathic pain who wish to avoid, or who cannot tolerate, oral treatments.

Treatments that should not be used

1.1.12 Do not start the following to treat neuropathic pain in non-specialist settings, unless advised by a specialist to do so:

- cannabis sativa extract
- capsaicin patch
- lacosamide
- lamotrigine
- levetiracetam
- morphine
- oxcarbazepine
- topiramate
- tramadol (this is referring to long-term use; see recommendation 1.1.10 for short-term use)
- venlafaxine.

European Journal of Neurology 2010, 17: 1113–1123 doi:10.1111/j.1468-1331.2010.02999.x

EFNS GUIDELINES

EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision

N. Attal[a,b], G. Cruccu[a,c], R. Baron[a,d], M. Haanpää[a,e], P. Hansson[a,f], T. S. Jensen[a,g] and T. Nurmikko[a,h]

Table 1 Classification of evidence for drug treatments in commonly studied neuropathic pain (NP) conditions and recommendations for use. Treatments are presented in alphabetical order. Only drugs used at repeated dosages are shown here (with the exception of treatments with long-lasting effects such as capsaicin patches). Drugs marked with an asterisk were found effective in single class II or III studies and are generally not recommended. Drugs marked with two asterisks are not yet available for use.

Aetiology	Level A rating for efficacy	Level B rating for efficacy	Level C rating for efficacy	Level A/B rating for inefficacy or discrepant results	Recommendations for first line	Recommendations for second or third line
Central pain[e]	Cannabinoids (oro-mucosal **, oral) (MS) Pregabalin (SCI)	Lamotrigine (CPSP) TCA (SCI, CPSP) Tramadol (SCI)* Opioids		Carbamazepine Gabapentin Lamotrigine (SCI) Levetiracetam Mexiletine S-ketamine iont. Valproate	Gabapentin Pregabalin TCA	Cannabinoids (MS) Lamotrigine Opioids Tramadol (SCI)

Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis

Nanna B Finnerup, Nadine Attal*, Simon Haroutounian, Ewan McNicol, Ralf Baron, Robert H Dworkin, Ian Gilron, Maija Haanpää, Per Hansson, Troels S Jensen, Peter R Kamerman, Karen Lund, Andrew Moore, Srinivasa N Raja, Andrew S C Rice, Michael Rowbotham, Emily Sena, Philip Siddall, Blair H Smith, Mark Wallace*

Lancet Neurol 2015; 162–73

	Total daily dose and dose regimen	Recommendations
Strong recommendations for use		
Gapabentin	1200–3600 mg, in three divided doses	First line
Gabapentin extended release or enacarbil	1200–3600 mg, in two divided doses	First line
Pregabalin	300–600 mg, in two divided doses	First line
Serotonin-noradrenaline reuptake inhibitors duloxetine or venlafaxine*	60–120 mg, once a day (duloxetine); 150–225 mg, once a day (venlafaxine extended release)	First line
Tricyclic antidepressants	25–150 mg, once a day or in two divided doses	First line†
Weak recommendations for use		
Capsaicin 8% patches	One to four patches to the painful area for 30-60 min every 3 months	Second line (peripheral neuropathic pain)‡
Lidocaine patches	One to three patches to the region of pain once a day for up to 12 h	Second line (peripheral neuropathic pain)
Tramadol	200–400 mg, in two (tramadol extended release) or three divided doses	Second line
Botulinum toxin A (subcutaneously)	50–200 units to the painful area every 3 months	Third line; specialist use (peripheral neuropathic pain)
Strong opioids	Individual titration	Third line§

GRADE=Grading of Recommendations Assessment, Development, and Evaluation (see appendix for details about the GRADE classification). *Duloxetine is the most studied, and therefore recommended, of the serotonin-noradrenaline reuptake inhibitors. †Tricyclic antidepressants generally have similar efficacy (appendix); tertiary amine tricyclic antidepressants (amitriptyline, imipramine, and clomipramine) are not recommended at doses greater than 75 mg/day in adults aged 65 years and older because of major anticholinergic and sedative side-effects and potential risk of falls;[33] an increased risk of sudden cardiac death has been reported with tricyclic antidepressants at doses greater than 100 mg daily.[34]

MULTIPLE SCLEROSIS JOURNAL | MSJ

Topical Review

Pharmacological management of spasticity in multiple sclerosis: Systematic review and consensus paper

Susana Otero-Romero, Jaume Sastre-Garriga, Giancarlo Comi, Hans-Peter Hartung, Per Soelberg Sørensen, Alan J Thompson, Patrick Vermersch, Ralf Gold and Xavier Montalban

Multiple Sclerosis Journal

1–11

DOI: 10.1177/1352458516643600

Baclofen orale 6 studi randomizzati su 7 superiore a placebo. Classe II/III

Tizanidina dose media 12-24 mg 2 studi classe I, 2 studi classe II

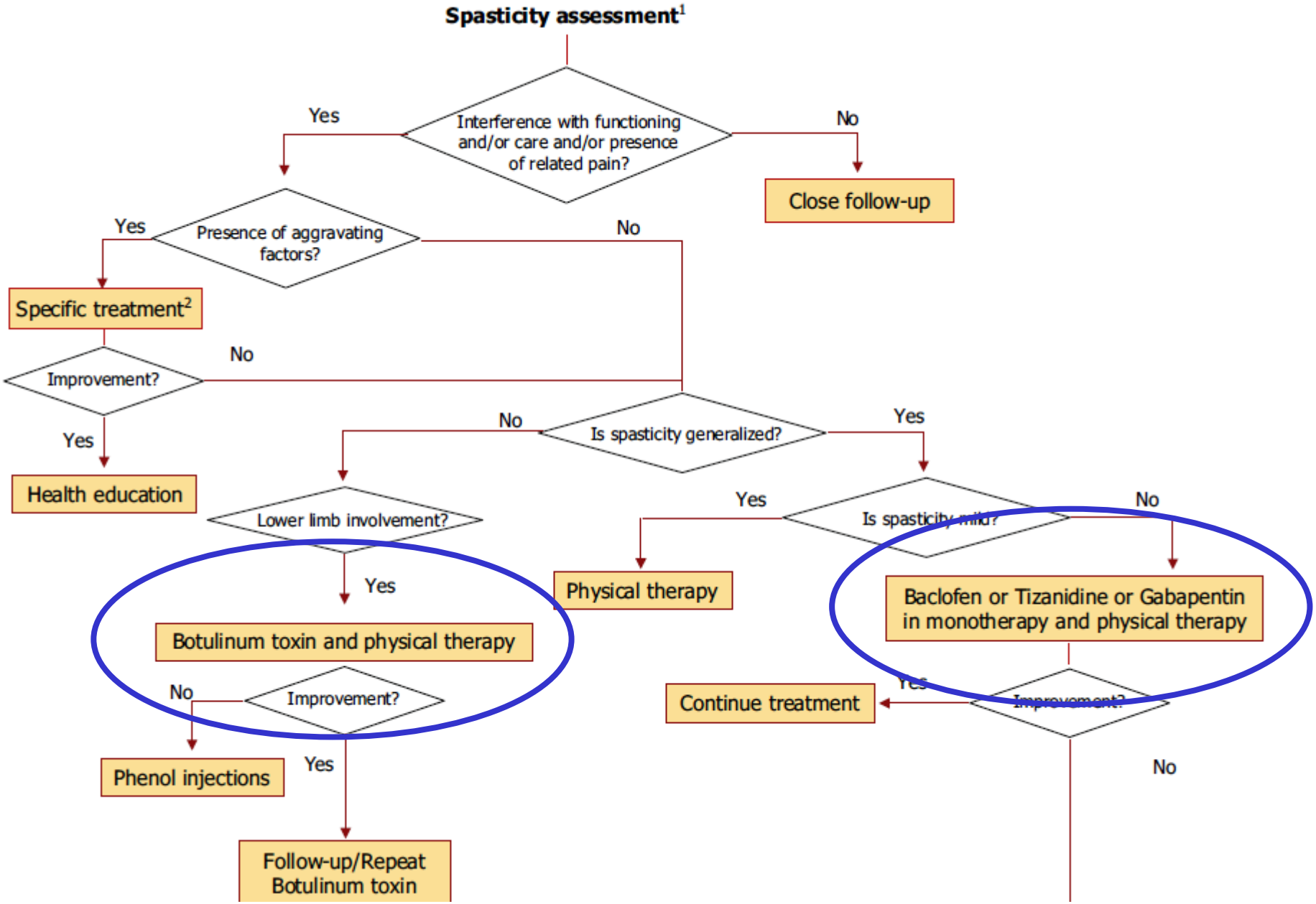
Diazepam no studi vs placebo in SM

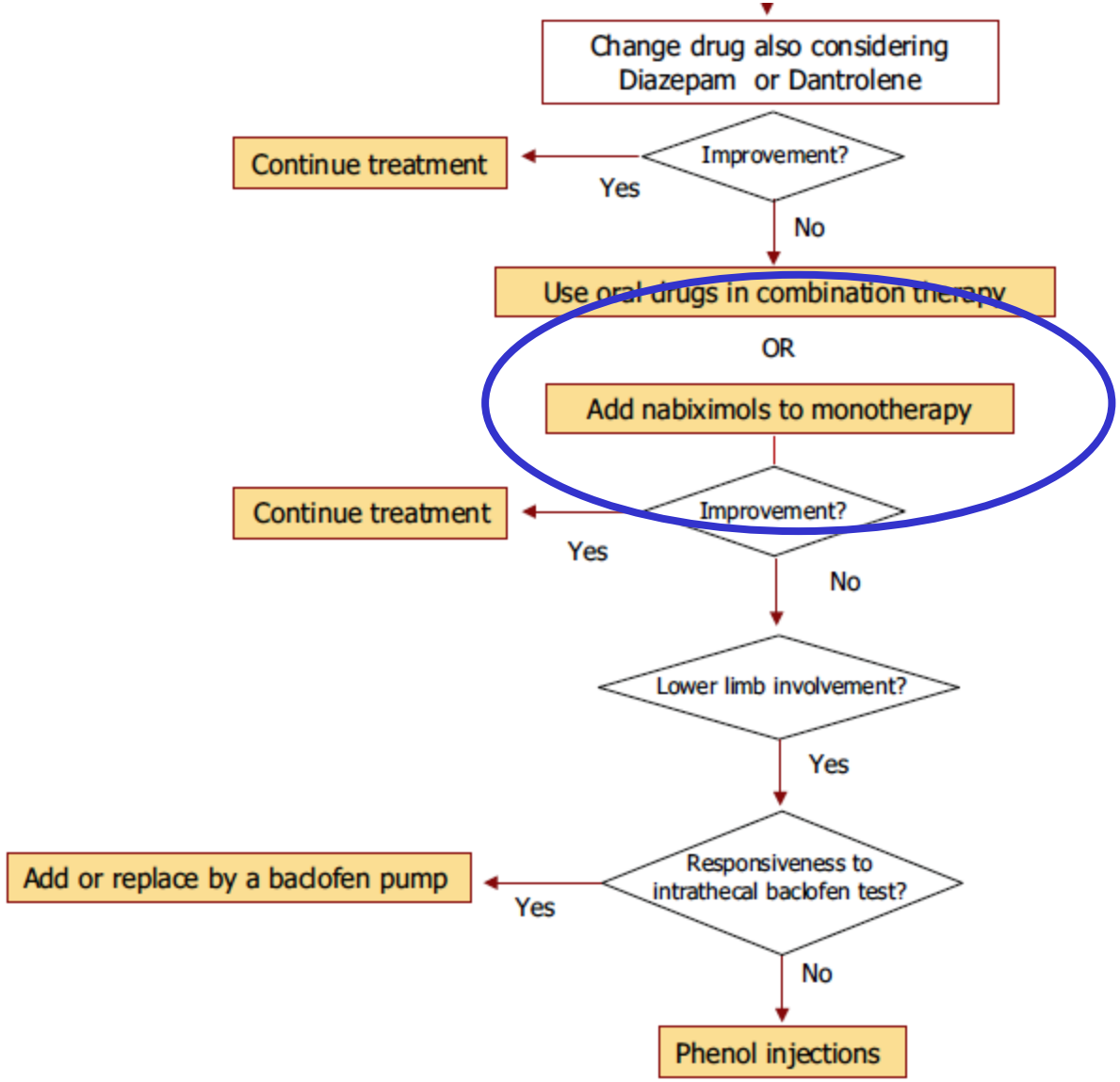
Gabapentin 2 studi classe II

Dantrolene 2 studi classe III

Estratto orale di cannabis 1 studio classe II (CAMS)

Nabiximol 3 studi classe I


Spasticity assessment[1]
Interference with functioning and/or care and/or presence of related pain?
Yes
No
Close follow-up
Presence of aggravating factors?
Yes
No
Specific treatment[2]
Improvement?
No
Yes
Health education
Is spasticity generalized?
No
Yes
Lower limb involvement?
Yes
Botulinum toxin and physical therapy
No
Improvement?
Phenol injections
Yes
Follow-up/Repeat Botulinum toxin
Physical therapy
Is spasticity mild?
Yes
No
Baclofen or Tizanidine or Gabapentin in monotherapy and physical therapy
Continue treatment
Improvement?
No


Change drug also considering Diazepam or Dantrolene
Improvement?
Yes
Continue treatment
No
Use oral drugs in combination therapy
OR
Add nabiximols to monotherapy
Improvement?
Yes
Continue treatment
No
Lower limb involvement?
Yes
Responsiveness to intrathecal baclofen test?
Yes
Add or replace by a baclofen pump
No
Phenol injections

Curr Neurol Neurosci Rep (2013) 13:320
DOI 10.1007/s11910-012-0320-5

DEMYELINATING DISORDERS (DN BOURDETTE AND V YADAV, SECTION EDITORS)

Pain and Multiple Sclerosis: Pathophysiology and Treatment

Claudio Solaro · Erika Trabucco · Michele Messmer Uccelli

There are more robust data for cannabinoids than for any other drugs for treating neuropathic pain in MS, although no head-to-head trial comparing them with other classic pain treatments has been conducted.

cannabinoidi

Derivati dalla pianta della cannabis

Combinazioni di due principi attivi:

delta9-tetraidrocannabinolo (THC)
Cannabidiolo (CBD)

THC effetto psicotropo

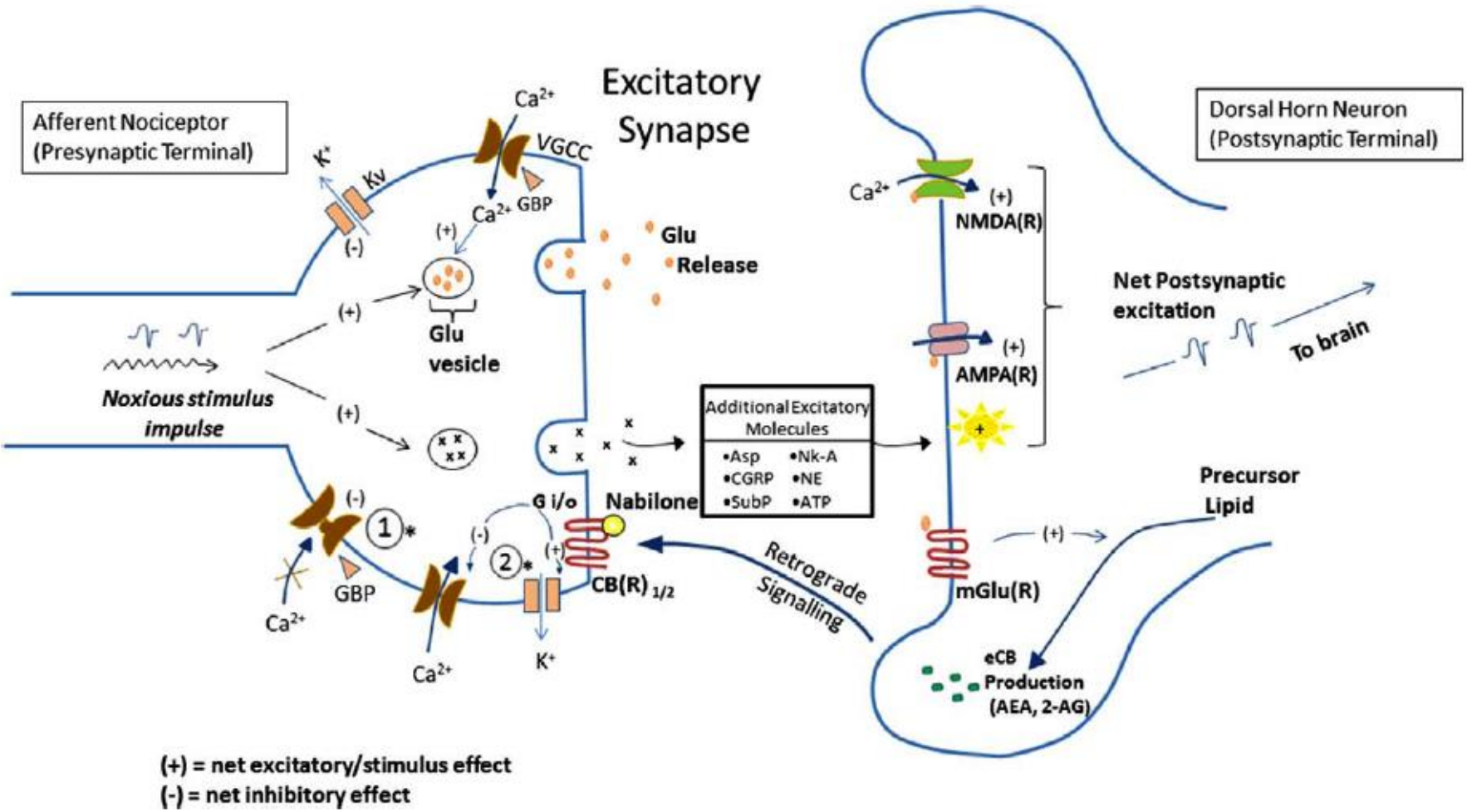
cannabinoidi

Azione agonista sui recettori cannabinoidi

CB1 (ippocampo, corteccia associativa, cervelletto, midollo, gangli dorsali, nervi periferici)

CB2 (periferia compreso tessuto linfatico e in basse concentrazioni encefalo)

cannabinoidi



SPECIAL ARTICLE

Systematic review: Efficacy and safety of medical marijuana in selected neurologic disorders

Report of the Guideline Development Subcommittee of the American Academy of Neurology

Barbara S. Koppel, MD, FAAN
John C.M. Brust, MD, FAAN
Terry Fife, MD, FAAN
Jeff Bronstein, MD, PhD
Sarah Youssof, MD
Gary Gronseth, MD, FAAN
David Gloss, MD

Correspondence to American Academy of Neurology: guidelines@aan.com

ABSTRACT

Objective: To determine the efficacy of medical marijuana in several neurologic conditions.

Methods: We performed a systematic review of medical marijuana (1948–November 2013) to address treatment of symptoms of multiple sclerosis (MS), epilepsy, and movement disorders. We graded the studies according to the American Academy of Neurology classification scheme for therapeutic articles.

Results: Thirty-four studies met inclusion criteria; 8 were rated as Class I.

Conclusions: The following were studied in patients with MS: (1) Spasticity: oral cannabis extract (OCE) is effective, and nabiximols and tetrahydrocannabinol (THC) are probably effective, for reducing patient-centered measures; it is possible both OCE and THC are effective for reducing both patient-centered and objective measures at 1 year. (2) Central pain or painful spasms (including spasticity-related pain, excluding neuropathic pain): OCE is effective; THC and nabiximols are probably effective. (3) Urinary dysfunction: nabiximols is probably effective for reducing bladder voids/day; THC and OCE are probably ineffective for reducing bladder complaints. (4) Tremor: THC and OCE are probably ineffective; nabiximols is possibly ineffective. (5) Other neurologic conditions: OCE is probably ineffective for treating levodopa-induced dyskinesias in patients with Parkinson disease. Oral cannabinoids are of unknown efficacy in non-chorea-related symptoms of Huntington disease, Tourette syndrome, cervical dystonia, and epilepsy. The risks and benefits of medical marijuana should be weighed carefully. Risk of serious adverse psychopathologic effects was nearly 1%. Comparative effectiveness of medical marijuana vs other therapies is unknown for these indications. *Neurology*® 2014;82:1556–1563

Table 1 Cannabinoid formulations

Generic name	Trade name	Manufacturer	Dosage and components	Study and dosage used of this formulation
Oral administration				
Cannabis extract	Cannador	IKF, Berlin, Germany	Ratio of Δ^9-THC 2.5 mg: CBD 1.25 mg	Mean 0.146 mg/kg/d up to maximum of 1.25 mg/kg/d (Carroll 2004[36]); mean 1.25 mg/kg/d up to maximum of 25 mg/d; maximum varied by weight (Zajicek 2003[7])
Cannabis extract	None	Not stated	Ratio of Δ^9-THC 2.5 mg: CBD 0.9 mg	Mean 0.146 mg/kg/d up to maximum of 0.25 mg/kg/d (Vaney 2004[5])
Cannabis extract	None	NIH, Bethesda, MD	100 mg CBD	100–300 mg/d (Cunha 1980[e2])
Cannabis extract	None	NIH, Bethesda, MD	100 mg CBD	10 mg/kg/d (Consroe 1991,[35] Curtis 2009[31])
Dronabinol	Marinol	Solvay Pharmaceuticals, Marietta, GA	2.5 mg Δ^9-THC	Maximum of 10 mg/d (Svendsen 2004,[25] Müller-Vahl 2003[40]); maximum of 25 mg/d (Freeman 2006,[28] Zajicek 2003[7])
Nabilone	Cesamet	Meda Pharmaceuticals, Somerset, NJ	100 mg CBD	100 mg (Curtis 2009[31]); 0.03 mg/kg (Fox 2002[29])
Oromucosal spray administration				
Nabiximols	Sativex	GW Pharmaceuticals, PLC, London, UK	Ratio of Δ^9-THC 2.7 mg: CBD 2.5 mg/spray	Mean 7.19 mg/d (Kavia 2010[26])
Nabiximols	Sativex	GW Pharmaceuticals, PLC, London, UK	Ratio of Δ^9-THC 2.7 mg: CBD 2.5 mg/spray	Dosage varied by study; maximum 65 mg/d (Collin 2010[10]); maximum 120 mg/d (Wade 2004[6])
Smoked (inhaled) marijuana				
Marijuana	None	Source not stated	4% THC	4 puffs (hits)/d (Corey-Bloom 2012[14]); 3.5%THC (Abrams 2007[e12]); 3.5%–7% (Wilsey 2008[e10]); 1%–8% THC (Ellis 2009[e13]); 0%–9.4% (Ware 2010[e14])

Abbreviations: CBD = cannabidiol, a major less-psychoactive resin extract constituent of the plant *Cannabis sativa L* (marijuana); THC = Δ-9-tetrahydrocannabinol, the principal psychoactive agent.

nabiximol

1 studio di classe I con 66 Pz: riduzione dolore 22% placebo, 41% farmaco

(Rog et al. Neurology 2005)

1 studio classe II con 337 Pz: riduzione dolore outcome secondario non raggiunto

(Collin et al. Neurol Res 2010)

OCE (oral cannabis extract)

1 studio di classe I con 630 Pz 14 settimane: riduzione dolore 30% placebo, 50% THC, 46% THC/CBD

(Zajieck et al, studio CAMS Lancet 2003)

1 studio classe I con 277 Pz: outcome secondario; riduzione dolore vs. placebo

(Zajieck et al, studio MUSEC J Neurol Neurosurg Psych 2012)

OCE (oral cannabis extract)

1 studio di classe I con 160 Pz 6 settimane: non significatività

(Vade et al. Mult Scler 2004)

1 studio classe I con 50 Pz 2 settimane: THC/CBD riduzione spasmi ai limiti della significatività

(Vaney et al, Mult Scler 2004)

Effetti collaterali

Overall, 1,619 patients were treated with cannabinoids for less than 6 months.
Meta-analysis of simple proportions yielded **6.9% (95% CI 5.7%–8.2%) who stopped the medication because of AEs.** Of the 1,118 who received placebo, 2.2% (95% CI 1.6%–3.5%) stopped because of AEs. Data on the symptoms that caused medication withdrawal were often incomplete.
Among patients treated with cannabinoids, the following symptoms appeared in at least 2 studies: **nausea, increased weakness, behavioral or mood changes (or both), suicidal ideation or hallucinations (or both), dizziness or vasovagal symptoms (or both), fatigue, feelings of intoxication**.
Psychosis, dysphoria, and anxiety are associated with higher concentrations of THC, which are not typical of the studies we analyzed.
There was one death “possibly related” to treatment (a seizure, followed by fatal aspiration pneumonia).

Summary of Systematic Review for **CLINICIANS**

AMERICAN ACADEMY OF NEUROLOGY®

EFFICACY AND SAFETY OF THE THERAPEUTIC USE OF MEDICAL MARIJUANA (CANNABIS) IN SELECTED NEUROLOGIC DISORDERS

This is a summary of the American Academy of Neurology (AAN) systematic review regarding the use of medical marijuana (cannabis) for treating selected neurologic disorders.

Please refer to the full systematic review at *AAN.com/guidelines* for more information, including a definition of the classification of evidence.

Forms of Cannabis

A variety of formulations were used in the studies examined, with differing amounts of tetrahydrocannabinol (THC) and cannabidiol (CBD): Some were pills, one was a mucosal spray, and some were vaporized or smoked. See Table 1 in the published systematic review for specific formulations.

What is the efficacy of using cannabinoids to treat central pain or painful spasms in MS?

Strong evidence	For patients with MS with central pain or painful spasms, OCE is effective for reduction of central pain (**2 Class I studies**).
Moderate evidence	THC or nabiximols (**1 Class I study each**) is probably effective for treating MS-related pain or painful spasms.
Insufficient evidence	Smoked marijuana is of unclear efficacy for reducing pain (**2 Class III studies that examined different issues**).

Summary of Systematic Review for **CLINICIANS**

AMERICAN ACADEMY OF NEUROLOGY®

EFFICACY AND SAFETY OF THE THERAPEUTIC USE OF MEDICAL MARIJUANA (CANNABIS) IN SELECTED NEUROLOGIC DISORDERS

This is a summary of the American Academy of Neurology (AAN) systematic review regarding the use of medical marijuana (cannabis) for treating selected neurologic disorders.

Please refer to the full systematic review at *AAN.com/guidelines* for more information, including a definition of the classification of evidence.

What is the efficacy of using cannabinoids to treat central pain or painful spasms in MS?

Strong evidence	For patients with MS with central pain or painful spasms, OCE is effective for reduction of central pain (**2 Class I studies**).
Moderate evidence	THC or nabiximols (**1 Class I study each**) is probably effective for treating MS-related pain or painful spasms.
Insufficient evidence	Smoked marijuana is of unclear efficacy for reducing pain (**2 Class III studies that examined different issues**).

June 23/30, 2015, Vol 313, No. 24 >

< Previous Article Next Article >

Original Investigation | June 23/30, 2015

Cannabinoids for Medical Use

A Systematic Review and Meta-analysis FREE

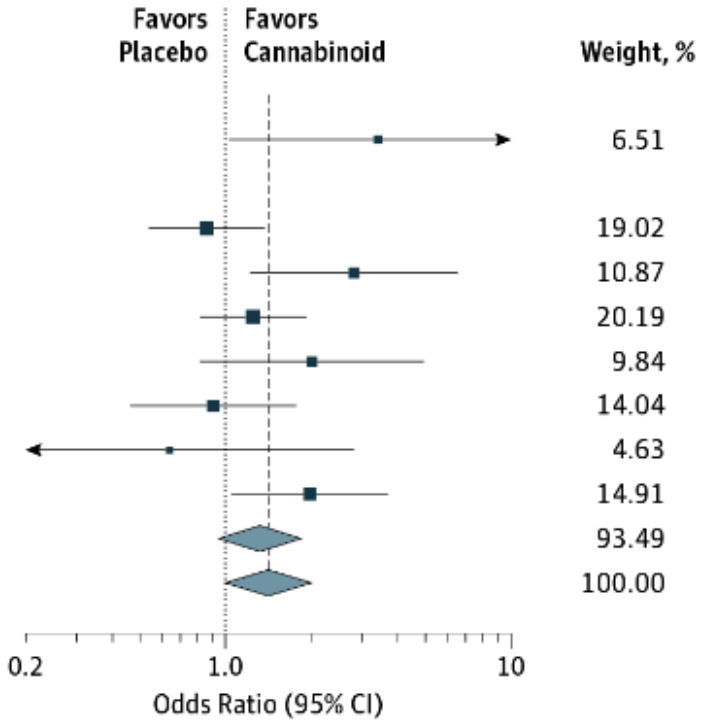
Penny F. Whiting, PhD[1,2,3]; Robert F. Wolff, MD[3]; Sohan Deshpande, MSc[3]; Marcello Di Nisio, PhD[4,5]; Steven Duffy, PgD[3]; Adrian V. Hernandez, MD, PhD[6,7]; J. Christiaan Keurentjes, MD, PhD[8]; Shona Lang, PhD[3]; Kate Misso, MSc[3]; Steve Ryder, MSc[3]; Simone Schmidlkofer, MSc[9]; Marie Westwood, PhD[3]; Jos Kleijnen, MD, PhD[3,10]

[+] Author Affiliations

JAMA. 2015;313(24):2456-2473. doi:10.1001/jama.2015.6358.

Text Size: A A

Improvement in Pain With Cannabinoid vs Placebo by Study	Cannabinoid Events No.	Cannabinoid Events Total No.	Placebo Events No.	Placebo Events Total No.	Odds Ratio (95% CI)
Tetrahydrocannabinol (smoked)					
Abrams et al,[77] 2007	13	25	6	25	3.43 (1.03-11.48)
Nabiximols					
GW Pharmaceuticals,[22] 2005	54	149	59	148	0.86 (0.54-1.37)
Johnson et al,[69] 2010	23	53	12	56	2.81 (1.22-6.50)
Langford et al,[65] 2013	84	167	77	172	1.25 (0.81-1.91)
Nurmikko et al,[76] 2007	16	63	9	62	2.00 (0.81-4.96)
Portenoy et al,[67] 2012	22	90	24	91	0.90 (0.46-1.76)
Selvarajah et al,[70] 2010	8	15	9	14	0.63 (0.14-2.82)
Serpell et al,[88] 2014	34	123	19	117	1.97 (1.05-3.70)
Subtotal $I^2 = 44.5\%$, ($P = .0.94$)	241	660	209	660	1.32 (0.94-1.86)
Overall $I^2 = 47.6\%$, ($P = .0.64$)	254	685	215	685	1.41 (0.99-2.00)



Evento: riduzione di almeno il 30% del dolore

Nabiximol vs. placebo

- riduzione media nella Numerical Rating Scale (NRS 0-10) -0.46 (6 trials)
- Riduzione media della neuropatic pain scale -3.89 (5 trials)
- Proporzione di pazienti con miglioramento alla “global impression of changiong score (OR 2.08, 6 trials)

June 23/30, 2015, Vol 313, No. 24 >

< Previous Article Next Article >

Original Investigation | June 23/30, 2015

Cannabinoids for Medical Use

A Systematic Review and Meta-analysis FREE

Penny F. Whiting, PhD[1,2,3]; Robert F. Wolff, MD[3]; Sohan Deshpande, MSc[3]; Marcello Di Nisio, PhD[4,5]; Steven Duffy, PgD[3]; Adrian V. Hernandez, MD, PhD[6,7]; J. Christiaan Keurentjes, MD, PhD[8]; Shona Lang, PhD[3]; Kate Misso, MSc[3]; Steve Ryder, MSc[3]; Simone Schmidlkofer, MSc[9]; Marie Westwood, PhD[3]; Jos Kleijnen, MD, PhD[3,10]

[+] Author Affiliations

JAMA. 2015;313(24):2456-2473. doi:10.1001/jama.2015.6358.

Text Size: A A

We conducted an extensive systematic review of the benefits and AEs associated with medical cannabinoids across a broad range of conditions. We included 79 RCTs (6462 participants), the majority of which evaluated nausea and vomiting due to chemotherapy or chronic pain and spasticity due to MS and paraplegia. Other patient categories were evaluated in fewer than 5 studies.

Most studies suggested that cannabinoids were associated with improvements in symptoms, but these associations did not reach statistical significance in all studies. Based on the GRADE approach, there was **moderate-quality evidence** to suggest that cannabinoids may be beneficial for the treatment of chronic neuropathic or cancer pain (smoked THC and nabiximols) and spasticity due to MS (nabiximols, nabilone, THC/CBD capsules, and dronabinol)

SPECIAL ARTICLE

Systematic review: Efficacy and safety of medical marijuana in selected neurologic disorders

Report of the Guideline Development Subcommittee of the American Academy of Neurology

Barbara S. Koppel, MD, FAAN
John C.M. Brust, MD, FAAN
Terry Fife, MD, FAAN
Jeff Bronstein, MD, PhD
Sarah Youssof, MD
Gary Gronseth, MD, FAAN
David Gloss, MD

Correspondence to American Academy of Neurology: guidelines@aan.com

ABSTRACT

Objective: To determine the efficacy of medical marijuana in several neurologic conditions.

Methods: We performed a systematic review of medical marijuana (1948–November 2013) to address treatment of symptoms of multiple sclerosis (MS), epilepsy, and movement disorders. We graded the studies according to the American Academy of Neurology classification scheme for therapeutic articles.

Results: Thirty-four studies met inclusion criteria; 8 were rated as Class I.

Conclusions: The following were studied in patients with MS: (1) Spasticity: oral cannabis extract (OCE) is effective, and nabiximols and tetrahydrocannabinol (THC) are probably effective, for reducing patient-centered measures; it is possible both OCE and THC are effective for reducing both patient-centered and objective measures at 1 year. (2) Central pain or painful spasms (including spasticity-related pain, excluding neuropathic pain): OCE is effective; THC and nabiximols are probably effective. (3) Urinary dysfunction: nabiximols is probably effective for reducing bladder voids/day; THC and OCE are probably ineffective for reducing bladder complaints. (4) Tremor: THC and OCE are probably ineffective; nabiximols is possibly ineffective. (5) Other neurologic conditions: OCE is probably ineffective for treating levodopa-induced dyskinesias in patients with Parkinson disease. Oral cannabinoids are of unknown efficacy in non-chorea-related symptoms of Huntington disease, Tourette syndrome, cervical dystonia, and epilepsy. The risks and benefits of medical marijuana should be weighed carefully. Risk of serious adverse psychopathologic effects was nearly 1%. Comparative effectiveness of medical marijuana vs other therapies is unknown for these indications. *Neurology*® 2014;82:1556–1563

Summary of Systematic Review for **CLINICIANS**

AMERICAN ACADEMY OF NEUROLOGY®

EFFICACY AND SAFETY OF THE THERAPEUTIC USE OF MEDICAL MARIJUANA (CANNABIS) IN SELECTED NEUROLOGIC DISORDERS

This is a summary of the American Academy of Neurology (AAN) systematic review regarding the use of medical marijuana (cannabis) for treating selected neurologic disorders.

Please refer to the full systematic review at *AAN.com/guidelines* for more information, including a definition of the classification of evidence.

Forms of Cannabis

A variety of formulations were used in the studies examined, with differing amounts of tetrahydrocannabinol (THC) and cannabidiol (CBD): Some were pills, one was a mucosal spray, and some were vaporized or smoked. See Table 1 in the published systematic review for specific formulations.

Do cannabinoids relieve spasticity in patients with multiple sclerosis (MS)?

Strong evidence	Oral cannabis extract (OCE) is established as effective for reducing patient-reported scores (**2 Class I studies**).
Moderate evidence	OCE is probably ineffective for reducing objective measures at 12 to 15 weeks (**1 Class I study**).
	THC is probably effective for reducing patient-reported scores (**1 Class I study**).
	THC is probably ineffective for reducing objective measures at 15 weeks (**1 Class I study**).
	Nabiximols is probably effective for reducing patient-reported symptoms at 6 weeks (**1 Class I study**) and probably ineffective for reducing objective measures at 6 weeks (**1 Class I study**).
Weak evidence	OCE is possibly effective for reducing objective measures at 1 year (**1 Class II study**).
	THC is possibly effective for reducing objective measures at 1 year (**1 Class II study**).
Insufficient evidence	Smoked marijuana is of uncertain efficacy (**insufficient evidence**).

Summary of Systematic Review for **CLINICIANS**

AMERICAN ACADEMY OF NEUROLOGY®

EFFICACY AND SAFETY OF THE THERAPEUTIC USE OF MEDICAL MARIJUANA (CANNABIS) IN SELECTED NEUROLOGIC DISORDERS

This is a summary of the American Academy of Neurology (AAN) systematic review regarding the use of medical marijuana (cannabis) for treating selected neurologic disorders.

Please refer to the full systematic review at *AAN.com/guidelines* for more information, including a definition of the classification of evidence.

Forms of Cannabis

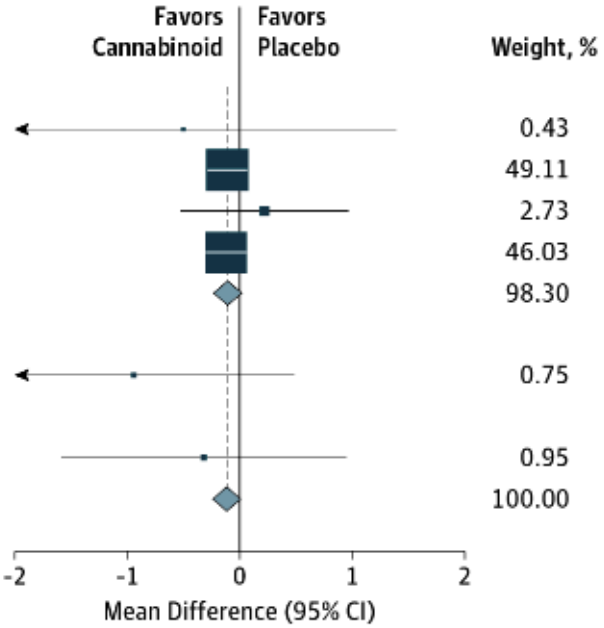
A variety of formulations were used in the studies examined, with differing amounts of tetrahydrocannabinol (THC) and cannabidiol (CBD): Some were pills, one was a mucosal spray, and some were vaporized or smoked. See Table 1 in the published systematic review for specific formulations.

Do cannabinoids relieve spasticity in patients with multiple sclerosis (MS)?

Strong evidence	Oral cannabis extract (OCE) is established as effective for reducing patient-reported scores (**2 Class I studies**).
Moderate evidence	OCE is probably ineffective for reducing objective measures at 12 to 15 weeks (**1 Class I study**).
	THC is probably effective for reducing patient-reported scores (**1 Class I study**).
	THC is probably ineffective for reducing objective measures at 15 weeks (**1 Class I study**).
	Nabiximols is probably effective for reducing patient-reported symptoms at 6 weeks (**1 Class I study**) and probably ineffective for reducing objective measures at 6 weeks (**1 Class I study**).
Weak evidence	OCE is possibly effective for reducing objective measures at 1 year (**1 Class II study**).
	THC is possibly effective for reducing objective measures at 1 year (**1 Class II study**).
Insufficient evidence	Smoked marijuana is of uncertain efficacy (**insufficient evidence**).

Change in Ashworth Score for Cannabinoid Compared With Placebo, Stratified According to Cannabinoid

Score Change With Cannabinoid vs Placebo by Study	Cannabinoid No. of Patients	Cannabinoid Mean (SD) Score Change	Placebo No. of Patients	Placebo Mean (SD) Score Change	Mean Difference (95% CI)	Weight, %
Nabiximols						
Collin,[125] 2010	156	-3.3 (9.25)	160	-2.8 (7.81)	-0.50 (-2.39 to 1.39)	0.43
Collin,[127] 2007	114	-.64 (.56)	63	-.53 (.58)	-0.11 (-0.29 to 0.07)	49.11
Wade,[129] 2004	73	-.37 (2.51)	70	-.59 (2.04)	0.22 (-0.53 to 0.97)	2.73
Berman,[87] 2007	40	-.13 (.43)	44	-.01 (.42)	-0.12 (-0.30 to 0.06)	46.03
Subtotal $I^2 = 0.0\%$, ($P = .0.82$)	383		337		-0.11 (-0.23 to 0.02)	98.30
Dronabinol						
Zajicek,[131] 2003	197	-1.86 (7.95)	207	-.92 (6.56)	-0.94 (-2.37 to 0.49)	0.75
Tetrahydrocannabinol/cannabidiol						
Zajicek,[131] 2003	207	-1.24 (6.6)	207	-.92 (6.56)	-0.32 (-1.59 to 0.95)	0.95
Overall $I^2 = 0.0\%$, ($P = .80$)	590		544		-0.12 (-0.24 to 0.01)	100.00



Nabilone (analogo THC) orale
Dronabinol (THC sintetico) orale

Nabiximol (Sativex) (THC:CBD 1:1) oro-mucoso

Cannabis Bedrocan THC 19%-CBD 1%
Bedica THC 14%-CBD 1%
Bedrobinol THC 12%-CBD 1%
Bediol THC 6%-CBD 7.5%

Nabiximol (Sativex)

THC+CBD in spray per mucosa orale

THC:CBD=1:1

Ogni puff 2.7 mg di THC e 2.5 mg di CBD

Dose 8-12 puff al dì

European Journal of Neurology 2011, **18:** 1122–1131 doi:10.1111/j.1468-1331.2010.03328.x

A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols* (Sativex®), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis

A. Novotna[a], J. Mares[b], S. Ratcliffe[c], I. Novakova[d], M. Vachova[e], O. Zapletalova[f], C. Gasperini[g], C. Pozzilli[h], L. Cefaro[i], G. Comi[j], P. Rossi[j], Z. Ambler[k], Z. Stelmasiak[l], A. Erdmann[m], X. Montalban[n], A. Klimek[o], P. Davies[p] and the Sativex Spasticity Study Group

572 Pz;

272 miglioramento del 20% nelle 4 settimane in singolo cieco

241 di questi randomizzati

Endpoint primario diffenza nella NRS (spasticity Numeric Rating Scale)

La differenza della NRS media tra i due gruppi è stata 0.84 punti (P = 0.0002)

O.R. riduzione del 30% 2.73 P = 0.0003

Meglio sonno, Barthel index, spasmi

ESTRATTO DI *CANNABIS SATIVA* IN SPRAY PER MUCOSA ORALE (SATIVEX®)

Indicazioni registrate

Trattamento per alleviare i sintomi in pazienti adulti affetti da spasticità da moderata a grave dovuta alla sclerosi multipla (SM) che non hanno manifestato una risposta adeguata ad altri medicinali antispastici e che hanno mostrato un miglioramento clinicamente significativo dei sintomi associati alla spasticità nel corso di un periodo di prova iniziale della terapia

ATC: N02BG10

Regime di fornitura: RNRL - Medicinale soggetto a prescrizione medica limitativa, da rinnovare volta per volta, vendibile al pubblico su prescrizione di centri ospedalieri o di specialisti – neurologo

Classe di rimborsabilità: H

Stupefacente: Tab II sez B

Procedura di registrazione: mutuo riconoscimento (procedura decentrata)

Prezzo

Spray per mucosa orale 3 flaconi nebulizzatori con pompa dosatrice da 10 ml – 90 erogazioni

Prezzo ex factory (IVA esclusa) € 440,00

Prezzo al pubblico (IVA inclusa) € 726,18

Accordo negoziale: payment by results a 4 settimane (100% rimborso) sui non responder definiti come mancato miglioramento di almeno il 20% del NRS + cost sharing al 50% a 6 settimane oppure 3 settimane gratuite per tutti gli eleggibili.

Eleggibilità e Dati Clinici

*SATIVEX è indicato come trattamento per alleviare i sintomi in pazienti affetti da spasticità da moderata a grave dovuta alla sclerosi multipla (SM) che non hanno manifestato una risposta adeguata ad altri farmaci antispastici e che hanno mostrato un miglioramento clinicamente significativo dei sintomi associati alla spasticità nel corso di un **periodo di prova iniziale** della terapia.*

O	Diagnosi	Sclerosi multipla	
O	Esordio di malattia (mesi)	...	
E	Il paziente assumerà Sativex in aggiunta ai trattamenti antispastici?	Si No (blocca)	
E	Il paziente è già trattato con antispastici?	Si No (blocca)	
O	Se Si indicare i farmaci:	Baclofen orale Tizanidina Dantrolene Eperisone Tiocolchicoside Altro	
	Se Altro indicare:	...	
O	Pregressi trattamenti antidolorifici	Gabapentin Pregabalin FANS Oppioidi Altro	
	Se Altro indicare:	...	
E	Numerical Rating Scale (NRS) per la spasticità	...	*4 ≤ valore NRS ≤ 10 e che verrà valutato nei Fup*
O	EDSS	..	*valori accettabili da 0-9,5*
O	Ambulation index	..	*valori da 0-9,0*
O	Test di 10 m (secondi)	***Effettuato***	
		Non effettuato per impossibilità del paziente, correlato ad una disabilità di grado elevato (≥6,5)	*controllo senza blocco con il valore dell'EDSS: presenza di alert*
O	Se effettuato inserire il valore (secondi)	...	
E	Il paziente presenta malattie cardiovascolari gravi	Si No	*blocca*
E	Il paziente presenta disturbi psichiatrici	Si No	*blocca*
E	Gravidanza	Si No	*blocca, campo solo per pazienti donne*
E	Il paziente assume sostanze psicoattive	Si	*blocca*

Rivalutazione

Si prega di fare riferimento al RCP di Sativex

http://www.mhra.gov.uk/Publications/PublicAssessmentReports/A-Zlisting/index.htm?indexChar=S

	RV1	**4ST**	*Sulla base di questa RV verrà applicato il PbR a 4ST (sui non responder)*
	RV2	**14ST**	

Le altre sono obbligatorie ogni 6 mesi

O	EDSS	...	*valori accettabili da 0-9,5*
O	Ambulation index	..	*valori accettabili da 0-9,0*
O	Test 10 metri (sec)	..	
E	**Numerical Rating Scale (NRS) per la spasticità**	...	*0 ≤ valore NRS ≤ 10 . Per valori < 20% in riferimento al basale interrompono il trattamento. Viene calcolato in automatico dal sistema tramite un delta dal valore basale di NRS riportato nella scheda E_DC*

O	*Si sono verificate reazioni nocive non volute al medicinale?*	Si No	*Link alla RNFV*
E	Il paziente continua il trattamento	Si No	*stop e inserire FT*

Agenzia Italiana del Farmaco
AIFA

MedDRa SOC	Molto comune ≥ 1/10	Comune da ≥ 1/100 a < 1/10	Non comune da ≥ 1/1000 a < 1/100
Infezioni e infestazioni			Faringite
Disturbi del metabolismo e della nutrizione		Anoressia (compresa perdita di appetito), maggiore appetenza	
Disturbi psichiatrici		Depressione, disorientamento, dissociazione, euforia	Allucinazioni (non specificate, uditive, visive), illusioni, paranoia, idee suicide, percezione delirante*
Patologie del sistema nervoso	Capogiri	Amnesia, disturbi dell'equilibrio, disturbi dell'attenzione, disartria, disgeusia, letargia, compromissione della memoria, sonnolenza	Sincope
Patologie dell'occhio		Visione annebbiata	
Patologie dell'orecchio e del labirinto		Vertigini	
Patologie cardiache			Palpitazioni, tachicardia
Patologie vascolari			Ipertensione
Patologie respiratorie, toraciche e mediastiniche			Irritazione alla gola
Patologie gastrointestinali		Costipazione, diarrea, secchezza delle fauci, glossodinia, ulcere della bocca, nausea, fastidio orale, dolore orale, vomito	Dolori addominali (superiori), discolorazione della mucosa orale*, disturbi della mucosa orale, esfoliazione della mucosa orale*, stomatite, discolorazione dentale
Patologie sistemiche e condizioni relative alla sede di somministrazione	Affaticamento	Dolore nel sito di applicazione, astenia, senso di anormalità, senso di ubriachezza, malessere	Irritazione del sito di applicazione
Lesioni, avvelenamento e disturbi dovuti alla procedura medica		Cadute	

Richiesta Farmaco

Si prega di fare riferimento al RCP di Sativex

Agenzia Italiana del Farmaco
AIFA

Una RF = Una confezione
Data RF ../../....

Testo fisso

Sativex è indicato solo per uso oromucosale.

Agitare il contenitore prima dell'uso e applicare lo spray in diversi siti della superficie oromucosale cambiando il sito di somministrazione ogni volta che il prodotto è utilizzato

Si richiede un ***periodo di titolazione*** per ottenere il dosaggio ottimale. Il numero e la frequenza delle applicazioni dello spray variano da paziente a paziente.

Giorno	N° applicazioni spray mattutine	N° applicazioni spray serali	N° applicazioni totali/ die
1	0	1	1
2	0	1	1
3	0	2	2
4	0	2	2
5	1	2	3
6	1	3	4
7	1	4	5
8	2	4	6
9	2	5	7
10	3	5	8
11	3	6	9
12	4	6	10
13	4	7	11
14	5	7	12

A completamento del periodo di titolazione, si consiglia ai pazienti di ***mantenere*** la dose ottimale ottenuta. La dose mediana somministrata negli studi clinici in pazienti affetti da sclerosi multipla è di otto applicazioni spray al giorno. Una volta ottenuto il dosaggio ottimale, i pazienti possono applicare la dose durante il corso della giornata a seconda della risposta e livello di tolleranza individuali. Aumenti o diminuzioni della dose potrebbero risultare appropriati in caso di alterazioni della gravità della malattia del paziente, cambiamenti delle terapie concomitanti somministrate o nel caso si manifestino fastidiose reazioni avverse. Dosaggi superiori a 12 applicazioni spray al giorno non sono raccomandati.

Multiple sclerosis in adults: management

Clinical guideline [CG186] Published date: October 2014

1.5.19 Consider baclofen or gabapentin[7] as a first–line drug to treat spasticity in MS depending on contraindications and the person's comorbidities and preferences. If the person with MS cannot tolerate one of these drugs consider switching to the other.

1.5.20 Consider a combination of baclofen and gabapentin[7],[8] for people with MS if:

- individual drugs do not provide adequate relief **or**
- side effects from individual drugs prevent the dose being increased.

1.5.21 Consider tizanidine or dantrolene as a second–line option to treat spasticity in people with MS.

1.5.22 Consider benzodiazepines as a third–line option to treat spasticity in MS and be aware of their potential benefit in treating nocturnal spasms.

1.5.23 Do not offer Sativex to treat spasticity in people with MS because it is not a cost effective treatment[9].

[7] At the time of publication (October 2014), gabapentin did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

MINISTERO DELLA SALUTE

DECRETO 9 novembre 2015

Funzioni di Organismo statale per la cannabis previsto dagli articoli 23 e 28 della convenzione unica sugli stupefacenti del 1961, come modificata nel 1972. (15A08888)

(GU n.279 del 30-11-2015)

IL MINISTRO DELLA SALUTE

Visto il decreto del Presidente della Repubblica 9 ottobre 1990, n. 309, di approvazione del Testo Unico delle leggi in materia di disciplina degli stupefacenti e sostanze psicotrope, prevenzione, cura e riabilitazione dei relativi stati di tossicodipendenza, e

In considerazione delle evidenze scientifiche fino ad ora prodotte, che dovranno essere aggiornate ogni due anni, si puo' affermare che l'uso medico della cannabis non puo' essere considerato una terapia propriamente detta, bensi' un trattamento sintomatico di supporto ai trattamenti standard, quando questi ultimi non hanno prodotto gli effetti desiderati, o hanno provocato effetti secondari non tollerabili, o necessitano di incrementi posologici che potrebbero determinare la comparsa di effetti collaterali.

Gli impieghi di cannabis ad uso medico riguardano:

l'analgesia in patologie che implicano spasticita' associata a dolore (sclerosi multipla, lesioni del midollo spinale) resistente alle terapie convenzionali (Lynch 2015; Koppel et al. 2014; Corey-Bloom et al. 2012; Rog et al. 2007; Ibegdu et al., 2012 Giacoppo et al. 2014; Aggarwal et al., 2007;);

l'analgesia nel dolore cronico (con particolare riferimento al dolore neurogeno) in cui il trattamento con antinfiammatori non steroidei o con farmaci cortisonici o oppioidi si sia rivelato inefficace (Lucas 2012; Aggarwal 2009; Ellis et al. 2009; Abrams et al., 2009; Eisenberg et al. 2014; Wilsey et al., 2013);

l'effetto anticinetosico ed antiemetico nella nausea e vomito, causati da chemioterapia, radioterapia, terapie per HIV, che non puo' essere ottenuto con trattamenti tradizionali (Tramer et al. 2001; Smith 2011; Cinti, 2009);

l'effetto stimolante dell'appetito nella cachessia, anoressia, perdita dell'appetito in pazienti oncologici o affetti da AIDS e nell'anoressia nervosa, che non puo' essere ottenuto con trattamenti standard (Beal et al, 1995; Beal et al. 1997; Carter et al. 2004; Haney et al. 2007);

l'effetto ipotensivo nel glaucoma resistente alle terapie convenzionali (Tomida et al 2004; Tomida et al2006);

la riduzione dei movimenti involontari del corpo e facciali nella sindrome di Gilles de la Tourette che non puo' essere ottenuta con trattamenti standard (Müller-Vahl, 2013).

REGIONE PIEMONTE

DIREZIONE SANITÀ
Settore ASSISTENZA FARMACEUTICA INTEGRATIVA E PROTESICA
settore.farmaceutico@regione.piemonte.it

Il Dirigente

Torino, 24 MAR. 2016

Protocollo n. 7058/A1404A

Classificazione 14 120 40

Ai Direttori Generali
Aziende Sanitarie Regionali

LORO SEDI

Oggetto: DGR n.24-2920 del 15 febbraio 2016 – indicazioni operative

Il Servizio Sanitario Regionale assume a proprio carico la spesa per l'erogazione di detti medicinali, come specificato dalla D.G.R. n. 24-2920 del 15 febbraio 2016, quando tale trattamento sia ritenuto dal medico indispensabile, per le indicazioni patologiche individuate nel punto 4.1 dell'Allegato tecnico al Decreto Ministeriale citato, ovvero:

1. analgesia in patologie che implicano spasticità associata a dolore (sclerosi multipla, lesioni del midollo spinale) resistente alle terapie convenzionali;
2. analgesia nel dolore cronico (con particolare riferimento al dolore neurogeno) in cui il trattamento con antinfiammatori non steroidei o con farmaci cortisonici o oppioidi si sia rivelato inefficace;
3. effetto anticinetosico ed antiemetico nella nausea e vomito, causati da chemioterapia, radioterapia, terapie per HIV, che non può essere ottenuto con trattamenti tradizionali;
4. effetto stimolante l'appetito nella cachessia, anoressia, perdita dell'appetito in pazienti oncologici o affetti da AIDS e nell'anoressia nervosa, che non può essere ottenuto con trattamenti standard;
5. effetto ipotensivo nel glaucoma resistente alle terapie convenzionali;
6. riduzione dei movimenti involontari del corpo e facciali nella *sindrome di Gilles de la Tourette* che non può essere ottenuta con trattamenti standard.

L'erogazione con onere a carico del Servizio Sanitario Regionale di tali medicinali è prevista per pazienti residenti o domiciliati in Regione Piemonte.

Per quanto attiene l'**erogazione** con oneri a carico del SSR di tali medicinali essa è effettuata dalle farmacie ospedaliere delle Aziende Sanitarie Locali o Ospedaliere, sia nei casi di prescrizione da parte dei medici specialisti ospedalieri, che nei casi di prescrizione da parte dei Medici di Medicina Generale.

A tal proposito ogni Azienda Sanitaria Regionale deve individuare almeno una farmacia ospedaliera per l'allestimento dei preparati magistrali, nonché per la dispensazione dei medesimi ai pazienti.

I riferimenti della/e farmacia/e ospedaliere individuate dovranno essere comunicate al Settore Assistenza Farmaceutica, Integrativa e Protesica.

(Legge n. 94 - 8 aprile 1998- art. 5)

DATI MEDICO (stampatello)

Dott._____Indirizzo_____ Tel_____

☐ Medico Specialista Ospedaliero Cell_____
Struttura Ospedaliera_____ Reparto_____
☐ MMG
☐ Specialista convenzionato (specificare)_____

DATI PAZIENTE

Codice alfanumerico_____
Residente/Domiciliato in Regione Piemonte SI☐ NO☐ ASL di residenza_____
Sesso ☐ M ☐ F Età_____

R/ Cannabis Flos :

- **bedrocan:** titolato al 19% in THC e < 1% in CBD
- **altro (specificare)** _____

Una cartina da mg _____ Di tali n° _____
☐ Fase di titolazione *(per un max di 15 gg di terapia)*
☐ Mantenimento *(per un max di 30 gg di terapia)*

Posologia e modo di somministrazione _____
_____(dosaggio massimo 2g/die)

Modalita' di assunzione ☐ **via orale** ☐ **via inalatoria** (con specifico vaporizzatore)

Motivazione del trattamento ritenuto indispensabile (DGR n.24-2920-15 febbraio 2016):

- analgesia in patologie che implicano spasticità associata a dolore (sclerosi multipla, lesioni del midollo spinale) resistente alle terapie convenzionali;
- analgesia del dolore cronico (con particolare riferimento al dolore neurogeno) in cui il trattamento con FANS o con cortisonici o oppioidi si sia rilevato inefficace;
- effetto anticinetosico ed antiemetico nella nausea e nel vomito causati da chemioterapia, radioterapia, terapie per l'HIV, che non può essere ottenuto con trattamenti tradizionali;
- effetto stimolante l'appetito nella cachessia, anoressia, perdita dell'appetito in pazienti oncologici o affetti da AIDS e nell'anoressia nervosa, che non può essere ottenuto con trattamenti standard;
- effetto ipotensivo nel glaucoma resistente alle terapie convenzionali;
- riduzione dei movimenti involontari del corpo e facciali nella sindrome di Gilles de la Tourette che non può essere ottenuta con trattamenti standard.

L'impiego attuale della *cannabis* ☐ sostituisce ☐ integra il trattamento con terapia convenzionale

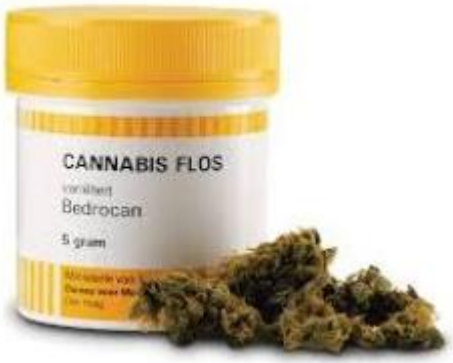
Esigenze particolari che giustificano la prescrizione di preparazione estemporanea
☐ Non esistono alternative terapeutiche
☐ Non esistono corrispondenti specialità in commercio

DICHIARA altresì che

Il medicinale verrà impiegato sotto la diretta responsabilità dello scrivente, previa informazione al paziente anche riguardante le modalità di somministrazione e dopo avere ottenuto il consenso informato dello stesso.

Luogo e data _____**Timbro e Firma (per esteso)**_____

bedrocan



19% THC

1% CBD

In decotto

dose usata da terapia antalgica 50 -100 mg 1-2 volte al dì

30 mg x 2-3 con latte (?)

Letteratura THC 10-20 mg/die

bedrocan

Costo alla farmacia ospedaliera 55€ 5 g

Costo/mese di terapia con 50 mg x 2= 33 €

Cannabinoids should be studied as other drugs are, to determine their efficacy, and when evidence is available, should be prescribed as other drugs are.

Pharmacological management of symptoms in multiple sclerosis: current approaches and future directions

Alan J Thompson, Ahmed T Toosy, Olga Ciccarelli

Lancet Neurol 2010; 9: 1182–99

Spasticità focale o generalizzata?

Ricadute funzionali (ad es. clono, dolore spasmi, retrazioni)?

La spasticità “compensa” l’ipostenia?

Sono presenti fattori scatenanti (infezioni, dolore)?

Possibilità di intervento fisioterapico?

Tabella 1 - Prodotti disponibili a base di Cannabinoidi (aggiornamento: agosto 2014)

Prodotto (Composizione)	Paese	Indicazione Terapeutica	Posologia
Sativex® 1 puff contiene 2,7 mg delta-9-THC + 2,5 mg CBD	Italia	Spasticità in SM	Iniziale titolazione del prodotto per 14 giorni, fino ad un massimo di 12 applicazioni/die. Proseguire con la dose ottimale (mediana: 8 applicazioni/die)
Bedrocan® (Fl 5 g di infiorescenze – THC 19% e CBD < 1%) **Bedica®** (Fl 5 g di infiorescenze – THC 14% e CBD < 1%) **Bedrobinol®** (Fl 5 g di infiorescenze – THC 12% e CBD < 1%) **Bediol®** (Fl 5 g di infiorescenze in granuli – THC 6% e CBD 7,5%)	Olanda	<u>Ci sono ragioni sufficienti per credere che la Cannabis medicinale possa aiutare in caso di</u>: - dolore e spasmi muscolari o crampi associati a sclerosi multipla o lesioni del midollo spinale - nausea, perdita di appetito, perdita di peso e debilitazione dovuti a cancro o AIDS - nausea e vomito associati a chemio o radioterapia per il trattamento di cancro, epatite C o HIV/AIDS - dolore cronico (principalmente associato al sistema nervoso, es. causato da lesioni ai nervi, dolore fantasma, nevralgie facciali o dolore cronico che rimane dopo il recupero da Herpes zoster) - sindrome di Gilles Tourette - glaucoma resistente alle terapie - altro	200 – 400 mg/die per preparare infuso o per vaporizzazione

CBD: Cannabidiolo; THC: Tetraidrocannabinolo