The use of medical-grade cannabis in patients non-responders to Nabiximols.

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Health Authorities Data Collection of THC:CBD Oromucosal Spray (L’Agenzia Italiana del Farmaco Web Registry): Figures after 1.5 Years.

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BACKGROUND: In Italy, all prescriptions for THC:CBD oromucosal spray for treatment of multiple sclerosis (MS) spasticity are linked to the official Agenzia Italiana del Farmaco (AIFA) web-based registry, which tracks the effectiveness and tolerability of medications in a prospective and observational manner.

METHODS: AIFA e-registry data for THC:CBD oromucosal spray collected between January 2014 and February 2015 for 1,534 patients from 30 large Italian specialized MS centres were compiled. Patients had a long disease history (17.6 ± 8.6 years) and significant impairment (mean Expanded Disability Status Scale score 6.4 ± 1.2). MS spasticity was evaluated using the 0-10 numerical rating scale (NRS).

RESULTS: After the first month titration and trial period, 61.9% of patients achieved sufficient improvement in spasticity (≥20% NRS) to qualify for continued treatment. After 6 months, clinically meaningful ≥30% NRS improvement was recorded in 40.2% of patients continuing with treatment. Spasticity-associated...
symptoms such as cramps and nocturnal spasms improved in most responding patients. Mean reported doses of THC:CBD oromucosal spray (6.2-6.7 sprays/day) were lower than those reported in clinical trials. Adverse events (mainly mild to moderate) were reported by 15% of patients; no new safety concerns beyond the approved label were identified.

CONCLUSION: The results of the AIFA e-registry analysis align with those of other THC:CBD observational projects and reaffirm the characteristics of this therapeutic option in the management of treatment-resistant MS spasticity, a frequently overlooked symptom.

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THC:CBD Observational Study Data: Evolution of Resistant MS Spasticity and Associated Symptoms.

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BACKGROUND: The prospective observational MObility ImproVEment (MOVE) 2 study is collecting real-life clinical outcomes data on patients with treatment-resistant multiple sclerosis (MS) spasticity treated with THC:CBD oromucosal spray in routine clinical practice. The MOVE 2 study has been ongoing in Italy, involving more than 30 MS centres across the country, since 2013.

METHODS: Web-based real-time data collection techniques are combined with traditional patients' diaries to capture a wide spectrum of outcomes associated with this innovative cannabis-based medication. After surpassing the recruitment threshold of 300 patients, an interim analysis was performed to determine whether the data collected to date align with those from MOVE 2-Germany and the largest phase III randomized controlled trial (RCT) of THC:CBD oromucosal spray.

RESULTS: In the Italian cohort, THC:CBD oromucosal spray was added mainly to oral baclofen. Similar to MOVE 2-Germany, during 3 months' observation, treatment discontinuations were limited and patients recorded meaningful improvements on the patient-based 0-10 numerical rating scale and physician-rated modified Ashworth scale at mean daily doses that were about one-third lower than those used in the RCT. Also, similar to MOVE 2-Germany, the proportion of patients reporting adverse events was about one-third of the rate recorded in the RCT.
CONCLUSIONS: While MOVE 2-Italy continues, this interim analysis has enabled us to better define the place in therapy of THC:CBD oromucosal spray within the context of daily management of our patients with MS spasticity.

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THC:CBD in Daily Practice: Available Data from UK, Germany and Spain.

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BACKGROUND: From the time Sativex (THC:CBD) oromucosal spray first became available in European Union countries in 2010 for the management of treatment-resistant multiple sclerosis (MS) spasticity, data from daily practice have been collected through various projects.

METHODS: A retrospective registry study and a prospective safety study of THC:CBD oromucosal spray are reported.

RESULTS: The most recent analysis of a retrospective registry established in the United Kingdom (UK), Germany and Switzerland, which collected safety data on more than 900 patients, has indicated a positive risk-benefit profile for THC:CBD oromucosal spray during long-term use. Long-term continuation rates were 68% (mean follow-up time 1 year) and the mean dose was 5.4 sprays/day. No new safety concerns were identified, and adverse events of special interest for a cannabis-based medicine were limited. The UK registry has since been closed but remains open in Germany and Switzerland. A prospective safety study undertaken in Spain involved 207 patients from 13 specialized MS centres who had been prescribed THC:CBD oromucosal spray. The findings aligned closely with the UK/German/Swiss registry data in terms of 1-year continuation rates (64.7%), mean daily dose (6.6 sprays/day) and safety profile, including no evidence of addiction, abuse or misuse.

CONCLUSIONS: The homogeneity between these observational studies supports the interest in THC:CBD oromucosal spray for management of MS spasticity in daily practice.

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Erratum in
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Summary for patients in

IMPORTANCE: As of March 2015, 23 states and the District of Columbia had medical marijuana laws in place. Physicians should know both the scientific rationale and the practical implications for medical marijuana laws.

OBJECTIVE: To review the pharmacology, indications, and laws related to medical marijuana use.

EVIDENCE REVIEW: The medical literature on medical marijuana was reviewed from 1948 to March 2015 via MEDLINE with an emphasis on 28 randomized clinical trials of cannabinoids as pharmacotherapy for indications other than those for which there are 2 US Food and Drug Administration-approved cannabinoids (dronabinol and nabilone), which include nausea and vomiting associated with chemotherapy and appetite stimulation in wasting illnesses.

FINDINGS: Use of marijuana for chronic pain, neuropathic pain, and spasticity due to multiple sclerosis is supported by high-quality evidence. Six trials that included 325 patients examined chronic pain, 6 trials that included 396 patients investigated neuropathic pain, and 12 trials that included 1600 patients focused on multiple sclerosis. Several of these trials had positive results, suggesting that marijuana or cannabinoids may be efficacious for these indications.

CONCLUSIONS AND RELEVANCE: Medical marijuana is used to treat a host of indications, a few of which have evidence to support treatment with marijuana and many that do not. Physicians should educate patients about medical marijuana to ensure that it is used appropriately and that patients will benefit from its use.

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Cannabinoids for Medical Use: A Systematic Review and Meta-analysis.


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Erratum in
JAMA. 2016 Apr 12;315(14):1522.
JAMA. 2015 Dec 1;314(21):2308.

Comment in

Summary for patients in

IMPORTANCE: Cannabis and cannabinoid drugs are widely used to treat disease or alleviate symptoms, but their efficacy for specific indications is not clear.
OBJECTIVE: To conduct a systematic review of the benefits and adverse events (AEs) of cannabinoids.
DATA SOURCES: Twenty-eight databases from inception to April 2015.

STUDY SELECTION: Randomized clinical trials of cannabinoids for the following indications: nausea and vomiting due to chemotherapy, appetite stimulation in HIV/AIDS, chronic pain, spasticity due to multiple sclerosis or paraplegia, depression, anxiety disorder, sleep disorder, psychosis, glaucoma, or Tourette syndrome.

DATA EXTRACTION AND SYNTHESIS: Study quality was assessed using the Cochrane risk of bias tool. All review stages were conducted independently by 2 reviewers. Where possible, data were pooled using random-effects meta-analysis.

MAIN OUTCOMES AND MEASURES: Patient-relevant/disease-specific outcomes, activities of daily living, quality of life, global impression of change, and AEs.

RESULTS: A total of 79 trials (6462 participants) were included; 4 were judged at low risk of bias. Most trials showed improvement in symptoms associated with cannabinoids but these associations did not reach statistical significance in all trials. Compared with placebo, cannabinoids were associated with a greater average number of patients showing a complete nausea and vomiting response (47% vs 20%; odds ratio [OR], 3.82 [95% CI, 1.55-9.42]; 3 trials), reduction in pain (37% vs 31%; OR, 1.41 [95% CI, 0.99-2.00]; 8 trials), a greater average reduction in numerical rating scale pain assessment (on a 0-10-point scale; weighted mean difference [WMD], -0.46 [95% CI, -0.80 to -0.11]; 6 trials), and average reduction in the Ashworth spasticity scale (WMD, -0.36 [95% CI, -0.69 to -0.05]; 7 trials). There was an increased risk of short-term AEs with cannabinoids, including serious AEs. Common AEs included dizziness, dry mouth, nausea, fatigue, somnolence, euphoria, vomiting, disorientation, drowsiness, confusion, loss of balance, and hallucination.

CONCLUSIONS AND RELEVANCE: There was moderate-quality evidence to support the use of cannabinoids for the treatment of chronic pain and spasticity. There was low-quality evidence suggesting that cannabinoids were associated with improvements in nausea and vomiting due to chemotherapy, weight gain in HIV infection, sleep disorders, and Tourette syndrome. Cannabinoids were associated with an increased risk of short-term AEs.

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Multiple sclerosis, cannabis, and cognition: A structural MRI study.

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OBJECTIVE: A subset of patients with multiple sclerosis (MS) smoke cannabis to relieve symptoms including spasticity and pain. Recent evidence suggests that smoking cannabis further impairs cognition in people with MS and is linked to impaired functional brain changes. No such association, however, has been reported between cannabis use and structural brain changes, hence the focus of the present study.

METHODS: Twenty patients with MS who smoke cannabis for symptom relief, and 19 matched non-cannabis-smoking MS patients were given the Brief Repeatability Neuropsychological Battery and structural MRI scans. Images were segmented into gray matter and white matter, and subsequently analysed with Partial Least Squares, a data-driven multivariate technique that explores brain-behaviour associations.

RESULTS: In both groups, the Partial Least Squares analysis yielded significant correlations between cognitive scores and both gray matter (33% variance, \( p < .0001 \)) and white matter (17% variance, \( p < .05 \)) volume. Gray matter volume in the thalamus, basal ganglia, medial temporal, and medial prefrontal regions, and white matter volume in the fornix correlated with cognitive deficits. Crucially, the analysis indicated that brain volume reductions were associated with more extensive cognitive impairment in the cannabis versus the non-cannabis MS group.

INTERPRETATION: These results suggest that cannabis use in MS results in more widespread cognitive deficits, which correlate with tissue volume in subcortical, medial temporal, and prefrontal regions. These are the first findings demonstrating an association between cannabis use, cognitive impairment and structural brain changes in MS patients.

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Medicinal use of cannabis and cannabinoids in older adults: where is the evidence?

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Limited range of indications for cannabis.

Wörz R.

Comment in
Dtsch Arztebl Int. 2013 Mar;110(10):175.

Comment on

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PMCID: PMC3607088
PMID: 23533550 [Indexed for MEDLINE]

Scientific data are lacking.
BACKGROUND: Spasticity is a common and poorly controlled symptom of multiple sclerosis. Our objective was to determine the short-term effect of smoked cannabis on this symptom.

METHODS: We conducted a placebo-controlled, crossover trial involving adult patients with multiple sclerosis and spasticity. We recruited participants from a regional clinic or by referral from specialists. We randomly assigned participants to either the intervention (smoked cannabis, once daily for three days) or control (identical placebo cigarettes, once daily for three days). Each participant was assessed daily before and after treatment. After a washout interval of 11 days, participants crossed over to the opposite group. Our primary outcome was change in spasticity as measured by patient score on the modified Ashworth scale. Our secondary outcomes included patients’ perception of pain (as measured using a visual analogue scale), a timed walk and changes in cognitive function (as measured by patient performance on the Paced Auditory Serial Addition Test), in addition to ratings of fatigue.

RESULTS: Thirty-seven participants were randomized at the start of the study, 30 of whom completed the trial. Treatment with smoked cannabis resulted in a reduction in patient scores on the modified Ashworth scale by an average of 2.74 points more than placebo (p < 0.0001). In addition, treatment reduced pain scores on a visual analogue scale by an average of 5.28 points more than placebo (p = 0.008). Scores for the timed walk did not differ significantly between treatment and placebo (p = 0.2). Scores on the Paced Auditory Serial Addition Test
decreased by 8.67 points more with treatment than with placebo (p = 0.003). No serious adverse events occurred during the trial.

INTERPRETATION: Smoked cannabis was superior to placebo in symptom and pain reduction in participants with treatment-resistant spasticity. Future studies should examine whether different doses can result in similar beneficial effects with less cognitive impact.

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PMCID: PMC3394820
PMID: 22586334 [Indexed for MEDLINE]


The therapeutic potential of cannabis and cannabinoids.

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Comment in
Dtsch Arztebl Int. 2013 Mar;110(10):175.

BACKGROUND: Cannabis-based medications have been a topic of intense study since the endogenous cannabinoid system was discovered two decades ago. In 2011, for the first time, a cannabis extract was approved for clinical use in Germany.

METHODS: Selective literature review.

RESULTS: Cannabis-based medications exert their effects mainly through the activation of cannabinoid receptors (CB1 and CB2). More than 100 controlled clinical trials of cannabinoids or whole-plant preparations for various indications have been conducted since 1975. The findings of these trials have led to the approval of cannabis-based medicines (dronabinol, nabilone, and a cannabis extract [THC:CBD=1:1]) in several countries. In Germany, a cannabis extract was approved in 2011 for the treatment of moderate to severe refractory spasticity in multiple sclerosis. It is commonly used off label for the treatment of anorexia, nausea, and neuropathic pain. Patients can also apply for government permission to buy medicinal cannabis flowers for self-treatment under medical supervision. The most common side effects of cannabinoids are tiredness and dizziness (in more than 10% of patients), psychological effects, and dry mouth. Tolerance to these side effects nearly always develops within a short time. Withdrawal symptoms are hardly ever a problem in the therapeutic setting.

CONCLUSION: There is now clear evidence that cannabinoids are useful for the treatment of various medical conditions.
Marijuana has been used medically since antiquity. In recent years there has been a resurgence of interest in medical applications of various cannabis preparations. These drugs have been cited in the medical literature as potential secondary treatment agents for severe pain, muscle spasticity, anorexia, nausea, sleep disturbances, and numerous other uses. This article reviews the research literature related to medical applications of various forms of cannabis. Benefits related to medical use of cannabinoids are examined and a number of potential risks associated with cannabis use, both medical and recreational, are considered. There is a clearly identified need for further research to isolate significant benefits from the medical application of cannabinoids and to establish dosage levels, appropriate delivery mechanisms and formulations, and to determine what role, if any, cannabinoids might play in legitimate medical applications. It is also imperative to determine if reported dangers pose a significant health risks to users.

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BACKGROUND: Cannabis therapy has been considered an effective treatment for spasticity, although clinical reports of symptom reduction in multiple sclerosis (MS) describe mixed outcomes. Recently introduced therapies of combined Delta9-tetrahydrocannabinol (THC) and cannabidiol (CBD) extracts have potential for symptom relief with the possibility of reducing intoxication and other side effects. Although several past reviews have suggested that cannabinoid therapy provides a therapeutic benefit for symptoms of MS, none have presented a methodical investigation of newer cannabinoid treatments in MS-related spasticity. The purpose of the present review was to systematically evaluate the effectiveness of combined THC and CBD extracts on MS-related spasticity in order to increase understanding of the treatment's potential effectiveness, safety and limitations.

METHODS: We reviewed MEDLINE/PubMed, Ovid, and CENTRAL electronic databases for relevant studies using randomized controlled trials. Studies were included only if a combination of THC and CBD extracts was used, and if pre- and post-treatment assessments of spasticity were reported.

RESULTS: Six studies were systematically reviewed for treatment dosage and duration, objective and subjective measures of spasticity, and reports of adverse events. Although there was variation in the outcome measures reported in these studies, a trend of reduced spasticity in treated patients was noted. Adverse events were reported in each study, however combined THC and CBD extracts were generally considered to be well-tolerated.

CONCLUSION: We found evidence that combined THC and CBD extracts may provide therapeutic benefit for MS spasticity symptoms. Although some objective measures of spasticity noted improvement trends, there were no changes found to be significant in post-treatment assessments. However, subjective assessment of symptom relief did often show significant improvement post-treatment. Differences in assessment measures, reports of adverse events, and dosage levels are discussed.

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Medicinal use of cannabis in the United States: historical perspectives, current trends, and future directions.

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Cannabis (marijuana) has been used for medicinal purposes for millennia, said to be first noted by the Chinese in c. 2737 BCE. Medicinal cannabis arrived in the United States much later, burdened with a remarkably checkered, yet colorful, history. Despite early robust use, after the advent of opioids and aspirin, medicinal cannabis use faded. Cannabis was criminalized in the United States in 1937, against the advice of the American Medical Association submitted on record to Congress. The past few decades have seen renewed interest in medicinal cannabis, with the National Institutes of Health, the Institute of Medicine, and the American College of Physicians, all issuing statements of support for further research and development. The recently discovered endocannabinoid system has greatly increased our understanding of the actions of exogenous cannabis. Endocannabinoids appear to control pain, muscle tone, mood state, appetite, and inflammation, among other effects. Cannabis contains more than 100 different cannabinoids and has the capacity for analgesia through neuromodulation in ascending and descending pain pathways, neuroprotection, and anti-inflammatory mechanisms. This article reviews the current and emerging research on the physiological mechanisms of cannabinoids and their applications in managing chronic pain, muscle spasticity, cachexia, and other debilitating problems.

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Deficient mental own-body imagery in a neurological patient with out-of-body experiences due to cannabis use.

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In the present work, we report repeated out-of-body experiences (OBEs) in a patient with tetraplegia and severe somatosensory loss due to multiple sclerosis and predominant involvement of the cervical spinal cord. OBEs were experienced on a daily basis and induced by cannabis treatment that was started for severe spasticity with painful cramps and cloni. In order to investigate the link between OBEs and mental own-body imagery, the patient was asked to imagine himself in the position and visual perspective that is generally reported during OBEs, using front- and back-facing schematic human stimuli. Performance was measured before and after cannabis consumption. First, our data reveal that the patient was less accurate for back-facing than front-facing stimuli. This was found before and after cannabis consumption and is the opposite pattern to what is generally observed in healthy participants and in our control subjects (who did not use cannabis). We refer to this as lesion effect and argue that this relative facilitation for stimuli reflecting the position and visual perspective that is generally reported during OBEs might be due to recurrent and spontaneous own-body transformations during the patient's frequent OBEs. Secondly, we found a cannabis effect, namely a performance improvement in the back-facing condition while performance in the front-facing condition remained unchanged, after cannabis administration. We argue that cannabis administration may interfere with own-body imagery when reflecting the actual body position and only when associated with brain damage. Based on these data we propose an extended neurological model for own-body illusions including multisensory and sensorimotor mechanisms, cannabis consumption, and cortical and subcortical processing.

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