

Cannabinoids and spinal cord stimulation for the treatment of failed back surgery syndrome refractory pain

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Objective: This study aimed to evaluate pain and its symptoms in patients with failed back surgery syndrome (FBSS) refractory to other therapies, treated with a combination of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), in association with spinal cord stimulation (SCS).

Settings: Outpatients referred at Pain Unit of San Vincenzo Hospital in Taormina (Italy), between September 2014 and January 2016.

Subjects: Eleven FBSS patients diagnosed with neuropathic pain using the Douleur Neuropathique 4 questionnaire and suffering from moderate to severe chronic refractory pain, and undergoing treatment with SCS and a combination of THC/CBD for 12 consecutive months.

Materials and methods: All the included patients discontinued previous unsuccessful therapy at least 2 months before the beginning of the cannabinoid therapy, with the exception of the SCS that was continued. Patients received a fixed dosage of cannabinoid agonists (THC/CBD) that could be increased subjective to pain control response. A Brief Pain Inventory questionnaire was administered to measure pain and its interference with characteristic dimensions of feelings and functions. The duration of treatment with SCS and THC/CBD combination was 12 months.

Results: Effective pain management as compared to baseline result was achieved in all the cases studied. The positive effect of cannabinoid agonists on refractory pain was maintained during the entire duration of treatment with minimal dosage titration. Pain perception, evaluated through numeric rating scale, decreased from a baseline mean value of 8.18 ± 1.07 – 4.72 ± 0.9 by the end of the study duration (12 months) ($P < 0.001$).

Conclusion: The results indicate that cannabinoid agonists (THC/CBD) can have remarkable analgesic capabilities, as adjuvant of SCS, for the treatment of chronic refractory pain of FBSS patients.

Keywords: cannabinoids, delta-9-tetrahydrocannabinol, THC, cannabidiol, CBD, failed back surgery syndrome, FBSS, refractory pain, spinal cord stimulation, SCS, cannabis

Introduction

Failed back surgery syndrome (FBSS) is defined by the International Association for the Study of Pain as “a spinal pain of unknown origin either persisting despite surgical intervention or appearing after surgical intervention for spinal pain originally in the same topographical location”.¹ Several conditions have been identified as underlying causes for FBSS, such as epidural fibrosis, global or lateral canal stenosis, foraminal stenosis, retained disc fragment, recurrent disc herniation or degeneration, spinal instability, facet joint pain, sacroiliac joint pain, discitis, adhesive arachnoiditis, and

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others.² The percentage of the insurgency of chronic pain after spinal surgery varies significantly ranging from 5% to 74.6%, and the percentage of the need for re-operation is between 13.4% and 35%.³ Up to 20%–40% of patients who have undergone lumbar spine surgery experience FBSS.⁴ Nowadays, this syndrome affects ~0.02%–2% of the general population.⁵ The FBSS patients frequently suffer from moderate to severe chronic pain, associated with sensory and/or motor deficits, as well as other severe chronic pain syndromes associated with the persistence of low back pain, deterioration or recurrence of radiculopathy, and sphincter dysfunction.^{6,7} The current therapeutic strategies for FBSS include antidepressant medications, antiepileptic medications,⁸ deep brain stimulation, spinal cord stimulation (SCS),^{9,10} epidural and intrathecal injections,^{11,12} spine surgery,¹³ counseling,¹⁴ and exercise therapy.¹⁵ FBSS is considered an intractable syndrome when various combinations of the existing therapeutic strategies prove ineffective. Opioids and their major adjuvants usually produce positive results in the treatment of chronic pain, especially when other therapeutic approaches fail. There is an increasing demand for alternative therapeutic strategies by patients and clinicians when available therapies are marginally effective, or not well tolerated. In this context, the authors assessed the effectiveness of an alternative approach for chronic refractory pain associated with FBSS, using cannabinoids as a multimodal treatment approach to neuropathic pain. The plant *Cannabis sativa* L. has been used for centuries, both for recreational and medicinal purposes. Only in recent times, studies about exogenous cannabinoids have been performed to evaluate their therapeutic value and to investigate the role of endogenous cannabinoids (endocannabinoids) in physiology and pathophysiology of many neurologic and neuropsychiatric diseases.^{16–18} Several types of insults which can damage the peripheral or central somatosensory nervous system, including FBSS, can cause neuropathic pain. It is estimated that 7%–8% of the population in developed nations is suffering from neuropathic pain.¹⁹ To date, therapeutic options for neuropathic pain induced by FBSS achieve effective analgesia in only less than 50% of the cases.²⁰ This pain could, however, be effectively treated by drugs modulating endocannabinoid system.²¹ This system is highly expressed in neurons and immune cells, and it plays a crucial role in the development of neuropathic pain.²² This pilot study aimed to evaluate the effect of a combination of delta-9-tetrahydrocannabinol (THC)/cannabidiol (CBD) in FBSS refractory to other available therapeutic strategies, including opioids, adjuvant drugs, radio frequency neuro-modulating treatments, and SCS alone. The SCS, a treatment

modality for chronic pain that has been in use since 1967,⁹ is an expensive therapy and careful selection for its suitability is recommended. Remarkable technological advances over the years have resulted in electrodes transitioning from single to multi-contact arrays and stimulators from external radiofrequency coupled to implantable rechargeable devices. Current implantable SCS electrodes can be inserted percutaneously through a Tuohy needle using essentially the same technique as that used for an epidural catheter.²³ In this context, a retrospective study documenting the results obtained with oral administration of cannabinoids agonists, namely a combination of THC/CBD, in eleven refractory FBSS patients is presented.

Materials and methods

This article reports a retrospective study, performed at Pain Therapy Unit of San Vincenzo Hospital of Taormina, in collaboration with the Anesthesiology and Pain Therapy Unit and the Department of Biomedical and Dental Sciences and Morphofunctional Imaging of the University Hospital “G. Martino” of Messina. All outpatients included in the study were referred at the Pain Unit of San Vincenzo Hospital, during the period between September 2014 and January 2016. Treatments were performed in accordance with rules and ethical standards on human experimentation and the Declaration of Helsinki of 1964 (further revised in 2013). All the study participants gave written informed consent (including information on possible risks and side effects) for participation in the research study. Every precaution was taken to protect the privacy of patients. The retrospective study was approved by the Local Ethics Committee (Comitato Etico Interaziendale della Provincia di Messina) with protocol number 61/17, and the clinical study is registered with the number NCT03210766 (www.clinicaltrials.org). Between November 2014 and December 2015, authors included the clinical records of eleven FBSS patients suffering from moderate to severe chronic pain not responsive to other treatment regimens (including neuromodulating techniques), and considered eligible according to the inclusion and exclusion criteria established for the study. The patients, aged between 49 and 77 years (median age 61.18±10.26 years), were equally distributed (six males and five females) (Table 1). Primary inclusion criteria in this study were the diagnosis of FBSS refractory to other standard treatments. Patients who had not discontinued their previous oral analgesic therapy, at least 2 months before the beginning of the treatment with cannabinoid agonists, were excluded. The SCS therapy, unsatisfactory in terms of pain perception as observed from

Table 1 Characteristics of patients, DN4 score, and BPI's NRS score before (baseline) and after (final) treatment with THC/CBD combination for 12 consecutive months

Patient's characteristics and questionnaires	
Sex (M/F)	6/5
Age range (years)	49–77
Median age (years)	61.18±10.26
DN4 score	8.90±1.37
BPI baseline NRS score (no therapy, only SCS)	8.15±0.98
BPI final NRS score (SCS and cannabinoid agonists)	4.72±0.9*

Note: * $P<0.0001$ vs BPI baseline NRS score. Data presented as mean \pm SD unless otherwise indicated.

Abbreviations: DN4, Douleur Neuropathique 4; BPI, Brief Pain Inventory; NRS, numeric rating scale; SCS, spinal cord stimulation; THC, delta-9-tetrahydrocannabinol; CBD, cannabidiol.

baseline numeric rating scale (NRS) values, was not discontinued (Table 1). Cannabinoid agonists (THC/CBD) were administered in association with SCS for a treatment period of 12 consecutive months.

The neuropathic pain was assessed using the Douleur Neuropathique 4 (DN4) questionnaire in all the cases studied. The DN4 questionnaire consists of a total of ten items, of which seven items are related to the characteristics of pain (burning, painful cold, electric shocks) and its association with abnormal sensations (tingling, pins and needles, numbness, itching), and three items are related to neurological examination in the painful area (touch hyperesthesia, pinprick hyperesthesia, tactile allodynia). The value of 1 was given to each positive item, and 0 value to each negative item. The total score was calculated as the sum of all ten items and the cutoff value for the diagnosis of neuropathic pain was established as a total score of 4/10.²⁴ Basal DN4 scores of patients ranged from 7/10 to 10/10 (mean =8.9±1.37). The Brief Pain Inventory (BPI) allows patients to rate and refer the severity of their pain and the degree by which pain interferes with common dimensions of feelings and functions. The BPI was performed by all the patients both at the first visit and at the end of treatment (after 12 months). Initially developed to assess pain related to cancer, the BPI has shown to be an appropriate measure of pain caused by a wide range of clinical conditions. The BPI is a eleven-item questionnaire that consists of four 0–10 NRS items asking patients to rate their pain at its “worst in the last 24 hours”, “least in the last 24 hours”, “average”, and “actually”, with 0 indicating “no pain” and 10 representing “pain as bad as you could imagine”. The remaining seven BPI items probe the degree to which pain interferes with general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life, again using a 0–10 value scale. For these interference items, 0 (zero) represents “does not interfere” and 10 indicates “interferes completely”.²⁵ Baseline NRS

scores for average pain at visit ranged from 7 to 10 (mean =8.15±0.98) (Table 1). Patients were visited weekly in the first month and every 2 weeks for the entire study duration. All patients received an oleic suspension of THC (19%) and CBD (<1%), 25 mg/day for oral administration. The dosage of cannabinoid agonists could be increased, depending on the positive response to pain control.

Statistical analysis

The numerical data were expressed as the mean \pm standard deviation (SD). For each numerical parameter for basal observation and after treatment, we separately performed statistical comparison using the Mann–Whitney test. For each numerical parameter, considered separately for basal and final values, we performed a comparison between basal observation and after treatment to evaluate the existence of a statistically significant difference using the Wilcoxon test.

Results

In FBSS patients treated with the THC/CBD combination, an analgesic effect was achieved in four cases within the first month of treatment. The effect of cannabinoid agonists on refractory pain was maintained during the entire observation time with minimal dosage titration. The mean pain perception calculated using the NRS decreased from 8.18±1.07 at first visit to 4.72±0.9 at the end of the observational time in all cases (Table 2), thus indicating marked analgesia with the treatment. The THC/CBD combination significantly reduced burning sensation and paresthesia linked to FBSS. The BPI interference examination showed that all the patients reported improvement in the quality of sleep (11/11; $P<0.01$). Additionally, THC/CBD combination enhanced mood as indicated by the rise in baseline mean level of 5.54±0.52–3.63±0.5 by the end of the study period

Table 2 Brief Pain Inventory in failed back surgery syndrome (FBSS) among eleven patients treated with spinal cord stimulation alone, before (baseline) and after (final) 12 months, and treatment with THC/CBD, (N=11).

Brief Pain Inventory items	Baseline values	Final values	Statistics
General activities	6.72±0.90	3.63±0.67	$P<0.001$
Mood	5.54±0.52	3.63±0.50	$P<0.001$
Walking abilities	6.45±0.82	3.27±0.78	$P<0.001$
Normal work	5.90±0.94	3.27±0.46	$P<0.001$
Relations with other people	6.09±1.04	3.09±0.94	$P<0.001$
Sleep	6.09±1.44	3.90±1.30	$P<0.01$
Enjoyment of life	6.18±0.87	3.54±1.03	$P<0.001$

Note: Data shown as mean \pm SD.

Abbreviations: THC, delta-9-tetrahydrocannabinol; CBD, cannabidiol.

($P < 0.001$). Remarkably, similar results were obtained with every item on the questionnaire.

The maximum THC/CBD combination dose prescribed for all patients was 100 mg/day, while the minimum was 50 mg/day, with a mean dose of 68.5 mg/day. All adverse events were transient lasting from 30 minutes to a few hours, and not requiring medical care or suspension of therapy (Table 3). There were no reports of any severe adverse events.

Discussion

FBSS is a symptomatological syndrome, influenced by physical, psychological, and psychosocial factors that contribute to worsening individual quality of life. The pathological mechanism of intractable pain related to FBSS is complex and includes permanent inflammatory, neuropathic, and compressive processes, and in some cases are not susceptible to medical or surgical resolution.²⁶ Treatment for this category of patients aims to achieve relief from pain and consequently improve quality of life and daily activities. The diagnosis of FBSS through clinical history or history of spine operation is not always easy. Physicians should find the underlying causes of the pain and the mechanisms responsible for its maintenance and enforcement. Only an accurate diagnosis can potentially lead to the implementation of appropriate pain management strategies; this is particularly true for neuropathic pain (of radicular, ganglion, or spine origin) which is initiated by nervous system lesions or dysfunction and can be maintained by several different mechanisms. Moreover, neuropathic pain is more likely to be caused either by surgical treatment or associated diseases (comorbidity) and is more difficult to treat than nociceptive pain.⁴ Successful treatment outcomes are difficult to achieve for chronic pain which can, in the long run, adversely affect

the patient, health care services, and eventually the society. Although SCS can successfully induce analgesia initially, this has been observed to be relatively temporary, with the analgesia usually wearing out after 12–24 months,⁹ as in the presented study. In this scenario, the quick onset and prolonged analgesic effects obtained with cannabis-derived products seem to be independent of the effect of prior SCS therapy. From the results obtained, the superior analgesia combined with the low incidence of adverse events suggests that cannabis-derived products may be a valuable therapeutic option for chronic refractory pain associated with FBSS, in comparison to other drug classes including opioids. Cannabis-derived products have been used historically for chronic pain, and are attracting renewed pharmaceutical interest for analgesia. Epidemiological studies show that 10%–15% of patients suffering from chronic pain use cannabis to improve pain, sleep, and mood.¹⁸ Cannabinoid compounds mediate their pharmacological actions by binding to the cannabinoid receptors, namely cannabinoid type 1 receptor CB1 and cannabinoid type 2 receptor CB2. The CB1 receptors are located predominantly in the nervous system, while CB2 receptors are present in the immune cells.¹⁷ Moreover, several authors have described cannabinoid neurophysiological system as distinct but functionally similar to the opioid pain modulation system.²⁷ Recent clinical trials, investigating the effects of the newest formulations of synthetic and naturally derived cannabinoids, demonstrated their analgesic properties for refractory neurogenic pain, brachial plexus injuries, and chronic neuropathic pain.¹⁶ These studies suggest that the administration of cannabinoid agonists should be considered in patients suffering from chronic moderate to severe pain, especially when other less invasive treatments and opioid therapies fail, or when extreme adverse events are reported.²⁸ The plant genus *Cannabis* contains a complex mixture of phytochemicals (over 60 compounds) known as cannabinoids. Among the cannabinoids, the most investigated are the two major active chemical constituents, namely THC and CBD. Cannabinoids are mixed polyketides derived biosynthetically from malonyl-CoA and hexanoyl-CoA units prenylated with geranyl phosphate.²⁹ THC is the main psychoactive type of cannabinoid, whereas CBD is the major component of cannabis with a distinct pharmacological and psychotropic profile to THC. CBD ($C_{21}H_{30}O_2$) is a resorcinol-based compound devoid of the psychoactive effects of THC and, on the contrary, is believed to be able to attenuate the psychotomimetic effects induced by high dosages of THC. Selective CB2 agonists may reduce central effects, but these are not clinically available. The mechanism of action of CBD is complex and

Table 3 Adverse events related to treatments

Adverse events	Cases (N)
Drowsiness	4
Attention/concentration disorders	3
Dry mouth	2
Headache	2
Nausea/vomiting	2
Apathy	1
Puffy lips	1
Palpitations	1
Dizziness	1
Subjective sense of facial dysmorphism	1
Mood disorders	1
Forgetfulness	1
Increased urinary retention	1

not fully known since this molecule is a “multifaceted-target” drug interacting with several non-endocannabinoid systems such as receptors, ion channels, enzymes, and transporters.³⁰ CBD modulates the activity of many cellular effectors, including the receptors CB1 and CB2,³¹ GPR55,³² 5HT1A,³³ μ - and δ -opioid,³⁴ peroxisome proliferator-activated receptor gamma (PPAR γ),³⁵ the transient receptor potential subfamily V member 1 (TRPV1) cation channels,³⁶ and fatty acid amide hydrolase (FAAH).³⁷

In Italy and other European countries, only a single product consisting of a THC/CBD oromucosal spray has been authorized by the regulatory agency for the treatment of multiple sclerosis spasticity. However, other cannabis flower preparations may be prescribed for patients suffering from chronic pain conditions, refractory to conventional therapy. In the present study, orally administered oleic suspension of THC (19%) and CBD (<1%) was chosen chiefly because the pharmacokinetic data indicate that intake of “high content” of THC cannabis oil results in detectable plasma concentrations of THC as compared to ingestion of “low content” of THC cannabis oil or “mid-content” THC oil-containing capsules.³⁸ Additionally, the availability of the product and the simplicity offered by the oral route of administration for the oil suspension, in comparison to vaporization, were favorable factors in choosing this formulation. Due to the lack of precise information on efficacy and safety of the product, the study protocol involved an initial low dosage to be increased according to the patient response.

In the cases described in the present study, the analysis of results confirms the positive effects of treatment with THC/CBD in patients with refractory FBSS pain. Moreover, results from BPI examination show an improvement in mood and general activities as well ($P < 0.001$). Overall, THC/CBD combination was well tolerated and not associated with any severe side effects. However, the small number of cases and the lack of a control group are limiting factors for this study to assess a definitive effect and/or for the identification of patient population for which treatment with THC/CBD may be appropriate. The positive effect of THC on the quality of sleep, reported in our study, has already been observed by other authors,³⁹ and could perhaps positively influence pain perception. To the best of our knowledge, this is the first study reporting the beneficial effects of a combination of THC/CBD in FBSS refractory pain. Preliminary studies on cannabis and sleep suggest that CBD may have therapeutic effects on insomnia. Similar effects favoring sleep were observed

with THC; however, contradictory findings revealed that this compound decreases sleep latency and could impair sleep quality in the long term.⁴⁰ As a consequence, in our opinion, the effects of THC on pain may be independent of an effect on sleep. Finally, cannabis-derived products should be used cautiously in patients with a history of, or current anxiety or panic disorder, as well as for those with potential for reported dependence or abuse. Additionally, careful monitoring is advised for patients with depression and other psychiatric disorders.⁴¹

Conclusion

This is the first study that underlines the beneficial effects of cannabinoids for the treatment of FBSS. The results suggest that THC/CBD combination may represent an innovative and valid strategy to treat disabling symptoms represented by pain, nausea, and sleep disorders in FBSS patients. Furthermore, in these patients, cannabinoid treatment could positively contribute to an improved quality of life. Though cannabinoids can have common side effects such as dry mouth and drowsiness, the side effects profile of THC/CBD combination seems to be milder and well tolerated. The chief limiting factors of this study are the small number of cases of FBSS patients with intractable refractory pain and the lack of a control group, even though it is a general opinion that interpretation of results obtained with placebo-controlled trials may encounter difficulties because of the psychoactive effects of cannabis. Additionally, it must be noted that ethical rules in Italy are very restrictive, especially in the context of pain treatment.

Albeit the limitations, in all the cases reported, the beneficial effect obtained with cannabinoids in association with SCS demonstrate that SCS therapy alone may be not sufficient to provide adequate analgesia.

Finally, we believe that prospective clinical studies are required to assess the real safety and efficacy of THC/CBD combination for chronic FBSS refractory pain. In conclusion, the current study suggest that THC/CBD combination represents an alternative treatment strategy in FBSS patients with chronic and severe pain, refractory to neuromodulating techniques, and is a valuable adjuvant to SCS.

Acknowledgment

Authors presented an earlier version of the abstract as a poster at the 38th Italian Society of Pharmacology (SIF) National Meeting in Rimini (Italy) in October 2017, prior to the actual completion or publication of the work.

Author contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

References

- Harvey AM. Classification of chronic pain – descriptions of chronic pain syndromes and definitions of pain terms. *Clin J Pain*. 1995;11(2):163.
- Slipman CW, Shin CH, Patel RK, et al. Etiologies of failed back surgery syndrome. *Pain Med*. 2002;3(3):200–214.
- Hussain A, Erdek M. Interventional pain management for failed back surgery syndrome. *Pain Pract*. 2014;14(1):64–78.
- Thomson S. Failed back surgery syndrome – definition, epidemiology and demographics. *Br J Pain*. 2013;7(1):56–59.
- Peul WC, van Houwelingen HC, van den Hout WB. Leiden – the Hague Spine Intervention Prognostic Study Group. Surgery versus prolonged conservative treatment for sciatica. *N Engl J Med*. 2007;356:2245–2256.
- Chan CW, Peng P. Failed back surgery syndrome. *Pain Med*. 2011;12(4):577–606.
- Baber Z, Erdek MA. Failed back surgery syndrome: current perspectives. *J Pain Res*. 2016;9:979–987.
- Prochazka J. T215 effect of gabapentin on neuropathic pain in failed back surgery syndrome. *Eur J Pain Suppl*. 2011;5(1):40.
- Abeloos L, de Witte O, Riquet R, Tuna T, Mathieu N. Évaluation à long terme de la stimulation médullaire dans les douleurs lombosciatiques neuropathiques postopératoires : étude rétrospective. [Long-term outcome of patients treated with spinal cord stimulation for therapeutically refractory failed back surgery syndrome: a retrospective study]. *Neurochirurgie*. 2011;57(3):114–119. French.
- Kumar K, North R, Taylor R, et al. Spinal cord stimulation vs. conventional medical management: a prospective, randomized, controlled, multicenter study of patients with failed back surgery syndrome (PROCESS Study). *Neuromodulation*. 2005;8(4):213–218.
- Demartini L, Stocco E, Bonezzi C. Failed back surgery syndrome and intrathecal drugs infusion. *Eur J Pain Suppl*. 2010;4(S4):299–301.
- Kumar K, Hunter G, Demeria DD. Treatment of chronic pain by using intrathecal drug therapy compared with conventional pain therapies: a cost-effectiveness analysis. *J Neurosurg*. 2002;97(4):803–810.
- Duggal N, Mendiondo I, Pares HR, et al. Anterior lumbar interbody fusion for treatment of failed back surgery syndrome: an outcome analysis. *Neurosurgery*. 2004;54(3):636–644.
- Esmer G, Blum J, Rulf J, Pier J. Mindfulness-based stress reduction for failed back surgery syndrome: a randomized controlled trial. *J Am Osteopath Assoc*. 2010;110(11):646–652.
- Mathews M, Mazhuvanchery C, Rab F. (562) Post laminectomy syndrome: treatment outcomes from a pain rehabilitation program. *J Pain*. 2014;15(4):S116.
- Lynch ME, Campbell F. Cannabinoids for treatment of chronic non-cancer pain: a systematic review of randomized trials. *Br J Clin Pharmacol*. 2011;72(5):735–744.
- Mannucci C, Navarra M, Calapai F, et al. Neurological aspects of medical use of cannabidiol. *CNS Neurol Disord Drug Targets*. 2017;16(5):541–553.
- Torrance N, Smith BH, Bennett MI, Lee AJ. The epidemiology of chronic pain of predominantly neuropathic origin. Results from a general population survey. *J Pain*. 2006;7(4):281–289.
- Attal N, Bouhassira D. Pharmacotherapy of neuropathic pain: which drugs, which treatment algorithms? *Pain*. 2015;156(Suppl 1):S104–S114.
- Finnerup NB, Sindrup SH, Jensen TS. The evidence for pharmacological treatment of neuropathic pain. *Pain*. 2010;150(3):573–581.
- Lynch ME, Ware MA. Cannabinoids for the treatment of chronic non-cancer pain: an updated systematic review of randomized controlled trials. *J Neuroimmune Pharmacol*. 2015;10(2):293–301.
- Maldonado R, Baños JE, Cabañero D. The endocannabinoid system and neuropathic pain. *Pain*. 2016;157(Suppl 1):S23–S32.
- Foletti A, Durrer A, Buchser E. Neurostimulation technology for the treatment of chronic pain: a focus on spinal cord stimulation. *Expert Rev Med Devices*. 2007;4(2):201–214.
- Attal N, Perrot S, Fermanian J, Bouhassira D. The neuropathic components of chronic low back pain: a prospective multicenter study using the DN4 Questionnaire. *J Pain*. 2011;12(10):1080–1087.
- Atkinson TM, Rosenfeld BD, Sit L, et al. Using confirmatory factor analysis to evaluate construct validity of the brief pain inventory (BPI). *J Pain Symptom Manage*. 2011;41:558–565.
- Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet*. 2006;367(9522):1618–1625.
- Pertwee RG. Targeting the endocannabinoid system with cannabinoid receptor agonists: pharmacological strategies and therapeutic possibilities. *Philos Trans R Soc Lond B Biol Sci*. 2012;367(1607):3353–3363.
- Ware MA, Doyle CR, Woods R, Lynch ME, Clark AJ. Cannabis use for chronic non-cancer pain: results of a prospective survey. *Pain*. 2003;102(1–2):211–216.
- Stout SM, Cimino NM. Exogenous cannabinoids as substrates, inhibitors, and inducers of human drug metabolizing enzymes: a systematic review. *Drug Metab Rev*. 2014;46(1):86–95.
- Fernández-Ruiz J, Sagredo O, Pazos MR, et al. Cannabidiol for neurodegenerative disorders: important new clinical applications for this phytocannabinoid? *Br J Clin Pharmacol*. 2013;75(2):323–333.
- Hayakawa K, Mishima K, Hazekawa M, et al. Cannabidiol potentiates pharmacological effects of delta(9)-tetrahydrocannabinol via CB(1) receptor-dependent mechanism. *Brain Res*. 2008;1188:157–164.
- Ryberg E, Larsson N, Sjögren S, et al. The orphan receptor GPR55 is a novel cannabinoid receptor. *Br J Pharmacol*. 2007;152(7):1092–1101.
- Russo EB, Burnett A, Hall B, Parker KK. Agonistic properties of cannabidiol at 5-HT1a receptors. *Neurochem Res*. 2005;30(8):1037–1043.
- Kathmann M, Flau K, Redmer A, Tränkle C, Schlicker E. Cannabidiol is an allosteric modulator of mu- and delta-opioid receptors. *Naunyn-Schmiedeberg Arch Pharmacol*. 2006;372(5):354–361.
- Esposito G, Scuderi C, Valenza M, et al. Cannabidiol reduces Aβ-induced neuroinflammation and promotes hippocampal neurogenesis through PPARγ involvement. *PLoS One*;2011(6):e28668.
- Costa B, Giagnoni G, Franke C, Trovato AE, Colleoni M. Vanilloid TRPV1 receptor mediates the antihyperalgesic effect of the nonpsychoactive cannabinoid, cannabidiol, in a rat model of acute inflammation. *Br J Pharmacol*. 2004;143(2):247–250.
- Bisogno T, Hanus L, de Petrocellis L, et al. Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. *Br J Pharmacol*. 2001;134(4):845–852.
- Goodwin RS, Gustafson RA, Barnes A, Nebro W, Moolchan ET, Huestis MA. Delta(9)-tetrahydrocannabinol, 11-hydroxy-delta(9)-tetrahydrocannabinol and 11-nor-9-carboxy-delta(9)-tetrahydrocannabinol in human plasma after controlled oral administration of cannabinoids. *Ther Drug Monit*. 2006;28(4):545–551.
- Blumenthal DE, Malesud CJ. Recent strategies for drug development in fibromyalgia syndrome. *Expert Rev Neurother*. 2016;16(12):1407–1411.
- Babson KA, Sottile J, Morabito D, Cannabis MD. Cannabis, cannabinoids, and sleep: a review of the literature. *Curr Psychiatry Rep*. 2017;19(4):23.
- Clark AJ, Lynch ME, Ware M, Beaulieu P, McGillveray IJ, Gourlay D. Guidelines for the use of cannabinoid compounds in chronic pain. *Pain Res Manag*. 2005;10(Suppl A):44A–46A.

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