Medical Cannabis in the Management of Opioid Dependence

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I am writing in enthusiastic support of the petition brought by Anita Briscoe to add management of opioid dependence to the list of conditions eligible for enrollment in the New Mexico Medical Cannabis Program.

Opioid dependence and its attendant morbidity and mortality have become a crisis in American health care. Between 2000 and 2014, the rate of opioid deaths in the United States increased 200 percent owing mostly to increases in prescription opiate overdoses (Rudd 2016). In New Mexico, 547 drug overdose deaths were recorded in 2014 by the CDC for an age-adjusted rate of 27.3 per 100,000 population (the second highest state rate in the nation after West Virginia). New Mexico was one of fourteen states in which the drug overdose rate increased (20.8 percent) in 2014 as compared to 2013. For the first time since consistent data have been available, the morbidity and mortality among white non-Hispanic Americans in the United States has increased in the period between 1999 and 2013, due largely to increases in suicides and overdose deaths (Case 2015).

There is mounting evidence that medical cannabis decreases population-level morbidity and mortality related to opioid dependence. In a study published by Bachhuber et al. in *JAMA Internal Medicine* in 2014, they compared trends in opioid overdose deaths between those states that had enacted medical cannabis programs compared to those states without those programs (Bachhuber 2014). They concluded, *"medical cannabis laws are associated with significantly lower state-level opioid overdose mortality rates."* Many clinicians who provide care to patients with severe chronic pain report that their patients have been able to significantly reduce or discontinue their use of opioid analgesics with the use of medical cannabis. The findings of Bachhuber et al. support the possibility that this manifests on a population level as a statewide-decline in overdose deaths. Indeed, in a recent paper by Bradford et al. where statewide Medicare Part D prescription rates were examined, it was "*found that the use of prescription drugs for which marijuana could serve as a clinical alternative fell significantly, once a medical marijuana law was implemented. National overall reductions in Medicare program and enrollee spending when states implemented medical marijuana laws were estimated to be $165.2 million in 2013. The availability of medical marijuana has a significant effect on prescribing patterns and spending in Medicare Part D.*" (Bradford 2016). These population-level findings are corroborated by a survey of chronic pain patients who were enrolled in the Michigan medical cannabis program (Boehnke 2016). Patients using medical cannabis as an adjunct to conventional

treatments reported a 64 percent reduction in opioid use and a decrease in medication side effects that affected everyday functioning. A survey of 410 Canadian medical cannabis patients by Lucas et al. (Lucas 2016) showed that 87 percent patients reported substituting cannabis for other drugs that they had been using including prescription medications (80.3 percent), alcohol (51.7 percent) and illicit drugs (32.6 percent).

A discussion of the role of medical cannabis in the management of opioid dependence requires a review of the role of medical cannabis in the management of chronic pain, since in many patients the two are inextricably linked.

Since the isolation of cannabinoid compounds from *Cannabis* sp. plants in 1965 (Mechoulam 1965; Budzikiewicz 1965), the identification of cannabinoid receptors in the central nervous system in 1990 (Matsuda 1990), and the isolation of the endogenous brain cannabinoid anandamide in 1992 (Devane 1992), the important role of endogenous and exogenous cannabinoids in modulating pain signaling and pain perception has been studied extensively. The modulation of pain transmission by cannabinoids in the CNS and peripheral nervous system occurs mainly through their action on the cannabinoid receptors called CB1, which are richly and widely distributed throughout the cortex, hippocampus, amygdala, basal ganglia and cerebellum (Herkenham 1990). Significantly, cannabinoid receptors are sparsely distributed in the lower brainstem regions that control respiratory and cardiovascular functions, accounting in part for the high therapeutic index and low fatal overdose potential that has been observed with the use of exogenous cannabinoids. Activation of CB1 receptors modifies neural transmission and pain perception in both acute and chronic pain through mechanisms that are independent of, but interact and are synergistic with, opioid receptors (Abrams 2011; Kazantzis 2016; Meng 1998; Scavone 2013).

In addition to their direct short-term effects upon neural transmission, cannabinoids also have important longer-term effects through modulating, or damping, neuroinflammatory processes that contribute to chronic pain states. These effects result from the modulation of both CB1 and CB2 receptors by both endogenous and exogenous cannabinoids (McPartland 2015). CB2 receptors are present in the body predominantly on cells of the immune system, and in the brain are present on microglial cells that mediate neuroinflammatory reactions (Mecha, 2016). Both of the major cannabinoids contained in marijuana (Δ^9-tetrahydrocannabinol and cannabidiol) have effects on modulating CB1 and CB2 receptors in the brain, and many of their effects appear to occur through physiological mechanisms that are independent of cannabinoid receptors. Cannabidiol (CBD) is of particular interest as an agent that could have beneficial effects in chronic neuroinflammatory states through its significant anti-inflammatory, anti-oxidant and neuroprotective properties. Although the effects of cannabidiol in mitigating neuroinflammation may be mediated in part through its action on cannabinoid receptors, much of its influence appear to occur through other (possibly GPR55 and other "orphan" receptors) mechanisms as these effects are not blocked by cannabinoid receptor antagonists. These actions likely occur through

complex interactions with microglial cells, modulating and dampening their pro-inflammatory tendencies through a "retrograde" process that down-regulates the expression of cellular inflammatory processes. [Alsasua del Valle 2006; Bisogno 2010; Booz 2011; Brotchie 2003; Croxford 2003; Downer 2011; Esposito 2006; Fagherazzi 2012; Fernández-Ruiz 2013; Froger 2009; García 2011; Glass 2001; Gowran 2011; Guzmán 2001; Hampson 2000; Hayakawa 2007; Iuvone 2009; Kozela 2011; Kwiatkoski 2012; Lastres-Becker 2005; Oddi 2012; Pacher 2012; Pope 2010; Pradhan 2013; Pryce 2003; Pryce 2012; Ramirez 2012; Rom 2013; Saito 2012; Scotter 2010; Skaper 1996; Skaper 2012; Touriño 2010; van der Stelt 2001; Zuardi 2008]. The effects of neuroinflammation on chronic pain are likely not limited to those diseases that have neurodegenerative processes as their underlying pathology (i.e., multiple sclerosis; Parkinson's disease). The neuropathic pain associated with spinal cord injury, for example, is now known to include a neuroinflammatory component (Walters 2014). Chronic pain and post-traumatic stress disorder (PTSD) are conditions that often co-exist. A recent study by Lerman et al. showed that standardized painful stimuli (capsaicin injections into the quadriceps muscle) elicited higher pain scores in PTSD patients as compared to controls and significantly higher levels of intrathecal pro-inflammatory cytokine IL-1β and delayed secretion of anti-inflammatory cytokine IL-10 (Lerman 2016). These finding suggest that microglial and astrocyte dysregulation contribute to the exaggerated pain response in the patients with PTSD.

Chronic stress and a patient's emotional state affect the perception of pain. In animal models, it has been demonstrated that stress modifies pain pathways in part through cannabinoid receptors, suggesting that this too is a mechanism by which cannabinoids have a positive impact upon chronic pain (Zheng 2015). Lee et al. demonstrated that the administration of purified Δ^9-tetrahydrocannabinol to human volunteers reduced the unpleasantness and intensity of capsaicin-induced pain and that this was associated with decreased activity in the anterior cingulate cortex and connectivity between the amygdala and the primary sensorimotor cortex (Lee 2013). In a recent survey of 100 consecutive patients returning for yearly recertification in the Hawai'i Medical Cannabis Program, 97 percent of whom were enrolled for chronic pain, the average reported decrease in pain was 64 percent (from 7.8 to 2.8 on a 1-10 scale) and 50 percent of patients also reported relief from stress and anxiety (Webb 2014).

In summary, endogenous and exogenous cannabinoids potentially affect pain perception through three general mechanisms: 1) direct action on neural transmission, mainly through action on CB1 receptors both in the central and peripheral nervous systems; 2) mitigation of neuroinflammatory processes associated with chronic pain, including actions on CB2 receptors; and 3) suppression of pathways between the anterior cingulate gyrus and the sensorimotor cortex that accentuate the perception of pain.

There are now many human clinical studies that support the efficacy of medical cannabis in the management of chronic pain (Abrams 2007; Abrams 2016; Aggarwal

2013; Haroutounian 2016; Jensen 2015; Lynch 2011; Mendoza Temple 2016; Wallace 2007; Ware 2015; Wilsey 2008; Wilsey 2013; Wilsey 2016). Three large meta-analyses on the subject have been published recently in major medical journals (Hill 2015; Koppel 2014; Whiting 2015).

The paper "Medical Marijuana for Treatment of Chronic Pain and Other Medical and Psychiatric Problems: A Clinical Review" by Kevin P. Hill MD appeared in the June 23/30, 2015, edition of *JAMA* (Hill 2015). Quoting from the paper:

"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."

Published in the same edition of *JAMA*, Whiting et al. (Whiting 2015) presented a different meta-analysis from that of Hill that reached similar conclusions:

"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, -0.24 to 0.01]; 5 trials)."

The Guideline Development Subcommittee of the American Academy of Neurology published their report of a systematic review of the efficacy of medical cannabis in neurologic disorders in the journal *Neurology* in 2014 (Koppel 2014):

"The following were studied in patients with MS: (1) Spasticity: oral cannabis extract (OCE) is effective, and nabiximols and tetrahydrocannbinol (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."

Even though the causes of chronic pain, the duration of pain, patient demographics, cannabinoid preparations, duration of treatment and outcomes measures varied between studies, there is a clear pattern of benefit from the use of medical cannabis in many (but not all) patients with severe chronic pain.

As with all medical treatments, there are adverse events observed with the use of medical cannabis. However, these do not appear to reach the level of severity that is commonly associated with the use of opioid analgesics. The most comprehensive longitudinal study of long-term cannabis use was published recently by Meier et al. in the journal *JAMA Psychiatry* (Meier 2016). They found that long-term cannabis use was associated with poorer periodontal health but not other significant poor health outcomes, as compared to long-term cigarette smoking which was associated with worse outcomes in periodontal health, lung function, markers of systemic inflammation, metabolic syndrome, blood lipid abnormalities, glycated hemoglobin and self-reported health. Because the management of severe chronic pain is complex and experience in treatment with medical cannabis is limited, it is advisable that an ongoing clinician-patient relationship be established that can carefully monitor treatment outcomes and adverse events. Canadian physicians have recently published draft guidelines titled "Prescribing smoked cannabis for chronic noncancer pain" that offers clinicians guidance in this area of clinical practice (Kahan 2014). Similar considerations would apply to the management of opioid dependence with medical cannabis.

Severe chronic pain is a condition that is currently eligible for enrollment in the New Mexico Medical Cannabis Program. However, there are many individuals with opioid dependence who do not have a current diagnosis of chronic pain who could benefit from enrollment in the Program. Many people in New Mexico are opioid dependent because their pain was managed with prescription opioid medications, often inappropriately, and opioid dependence can persist long after the pain has resolved. Many others are dependent because of psychological and sociological influences. The impact of opioid dependence is felt few places as acutely as New Mexico. A growing body of information from the chronic pain literature supports the role of medical cannabis in reducing the individual and population harms related to opioid dependence. The risk-benefit ratio for the use of medical cannabis in selected patients in this context is far more favorable for medical cannabis as compared to continuing opioid use. The addition of opioid dependence to the list of conditions eligible for enrollment in the New Mexico Medical Cannabis Program is entirely consistent with the spirit and the letter of the Lynn & Erin Compassionate Use Act. I urge the Medical Advisory Board to recommend addition of opioid dependence in its report to the Secretary of Health.

Citations

Abrams DI, Jay CA, Shade SB, Vizoso H, Reda H, Press S, Kelly ME, Rowbotham MC, Petersen KL. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. *Neurology* **68**:515-521 (2007).

Abrams DI, Couey P, Shade SB, Kelly ME, Benowitz NL. Cannabinoid-opioid interaction in chronic pain. *Clinical Pharmacology & Therapeutics* **90**:844-851 (2011).

Abrams DI. Integrating cannabis into clinical cancer care. *Current Oncology* **23**:S8-S14 (2016).

Aggarwal SK, Cannabinergic pain medicine: a concise clinical primer and survey of randomized-controlled trial results. *Clinical Journal of Pain* **29**:162-171 (2013).

Alsasua del Valle A. Implication of cannabinoids in neurological diseases. *Cellular & Molecular Neurobiology* **26**: 579-91 (2006).

Bachhuber MA, Saloner B, Cunningham CO, Barry CL. Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999 – 2010. *JAMA Internal Medicine* **174**:1668-1673 (2014).

Beal BR, Wallace MS. An overview of pharmacologic management of chronic pain. *Medical Clinics of North America* **100**:65-79 (2016).

Bisogno T, Di Marzo V. Cannabinoid receptors and endocannabinoids: role in neuroinflammatory and neurodegenerative disorders. *CNS & Neurologic Disorders - Drug Targets* **9**: 564-73 (2010).

Boehnke KF, Litinas E, Clauw DJ. Medical cannabis use is associated with decreased opiate medication use in a retrospective cross-sectional survey of patients with chronic pain. *Journal of Pain* **17**:739-744 (2016).

Booz GW. Cannabidiol as an emergent therapeutic strategy for lessening the impact of inflammation on oxidative stress. *Free Radical Biology & Medicine* **51**:1054-61 (2011).

Bradford AC, Bradford WE. Medical marijuana laws reduce prescription medication use in Medicare Part D. *Health Affairs* **35**:1230-1236 (2016).

Brotchie JM. CB_1 cannabinoid receptor signaling in Parkinson's disease. *Current Opinion in Pharmacology* **3**:54-61 (2003).

Budzikiewicz H, Alpin RT, Lightner DA, Djerassi C, Mechoulam R, Gaoni Y. Mass spectroscopy and its application to the structural and stereochemical problems. 68. Mass spectroscopic studies of the constituents of hashish. *Tetrahedron* **21**:1881-1888 (1965).

Case A, Deaton A. Rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21st century. *PNAS* **112**:15078-15083 (2015).

Chou R, Turner JA, Devine EB, Hansen RN, Sullivan SD, Blazina I, Dana T, Bougatsos C, Deyo RA. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. *Annals of Internal Medicine* **162**:276-286 (2015).

Croxford JL. Therapeutic potential of cannabinoids in CNS disease. CNS *Drugs* **17**:179-202 (2003).

Devane WA, Hanus L, Breuer A, Pertwee RG, Stevenson LA, Griffin G, Gibson D, Mandelbaum A, Etinger A, Mechoulam R. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science* **258**:1946-1949 (1992).

Downer EJ, Clifford E, Gran B, Nel HJ, Fallon PC, Moynagh PN. Identification of the synthetic cannabinoid R(+)WIN55,212-2 as a novel regulator of IFN regulatory factor 3 activation and IFN-β expression. *Journal of Biological Chemistry* **286**: 10316-10328 (2011).

Esposito G, De Filippis D, Maiuri MC, De Stefano D, Carnuccio R, Iuvone T. Cannabidiol inhibits inducible nitric oxide synthase protein expression and nitric oxide production in beta-amyloid stimulated PC12 neurons through p38 MAP kinase and NF-kappa B involvement. *Neuroscience Letters* **399**:91-95 (2006).

Fagherazzi EV, Garcia VA, Maurmann N, ,Bervanger T, Halmenschlager LH, Busato SB, Hallak JE, Zuardi AW, Crippa JA, Schröder N. Memory-rescuing effects of cannabidiol in an animal model of cognitive impairment relevant to neurodegenerative disorders. *Psychopharmacology* **219**:1133-1140 (2012).

Fernández-Ruiz J, Sagredo O, Pazos MR, García C, Pertwee R, Mechoulam R, Martínez-Orgado J. Cannabidiol for neurodegenerative disorders: important new clinical applications for this phytocannabinoid? *British Journal of Clinical Pharmacology* **75**:323-33 (2013).

Froger N Orellana JA, Cohen-Salmon M, Ezan P, Amigou E, Sáez JC, Giaume C. Cannbinoids prevent the opposite regulation of astroglial connexin43 hemichannels and gap junction channels induced by pro-inflammatory treatments. *Journal of Neurochemistry* **111**:1383-97 (2009).

García C, Palomo-Garo C, García-Arencibia M, Ramos JA, Pertwee RG, Fernández-Ruiz J. Symptom-relieving and neuroprotective effects of the phytocannabinoid Δ9-THCV in animal models of Parkinson's disease. *British Journal of Pharmacology* **163**:1495-1506 (2011).

Gaskin DJ, Richard P. The economic costs of pain in the United States. *Journal of Pain* **13**:715-724 (2012)

Glass M. The role of cannabinoids in neurodegenerative diseases. *Progress in Neuro-psychopharmacology & Biological Psychiatry* **25**:743-65 (2001).

Gowran A, Noonan J, Campbell VA. The multiplicity of action of cannabinoids: implications for treating neurodegeneration. *CNS Neuroscience & Therapeutics* **17**:637-44 (2011).

Guzmán M, Sánchez C, Galve-Roperh I. Control of the cell survival/death decision by cannabinoids. *Journal of Molecular Medicine (Berlin)* **78**:613-25 (2001).

Hampson AJ, Grimaldi M, Lolic M, Wink D, Rosenthal R, Axelrod J. Neuroprotective antioxidants from marijuana. *Annals of the New York Academy of Science* **899**:274-82 (2000).

Haroutounian S, Ratz Y, Ginosar Y, Furmanov K, Saifi F, Meidan R, Davidson E. The effect of medicinal cannabis on pain and quality of life outcomes in chronic pain: a prospective open-label study. *Clinical Journal of Pain* doi:10.1097/AJP.0000000000000364 (2016).

Hayakawa K, Mishima K, Nozako M, Hazekawa M, Irie K, Fujioka M, Orito K, Abe K, Hasebe N, Egashira N, Iwasaki K, Fujiwara M. Delayed treatment with cannabidiol has a cerebroprotective action via a cannabinoid receptor-independent myeloperoxidase-inhibiting mechanism. *Journal of Neurochemistry* **102**:1488-96 (2007).

Herkenham M, Lynn AB, Little MD, Johnson MR, Melvin LS, de Costa, BR, Rice KC. Cannabinoid receptor localization in brain. *PNAS* **87**:1932-1936 (1990).

Hill KP. Medical marijuana for treatment of chronic pain and other medical and psychiatric problems: a clinical review. *JAMA* **313**:2474-2483 (2015).

Iuvone T, Esposito G, De Filippis D, Scuderi C, Steardo L. Cannabidiol: a promising drug for neurodegenerative disorders? CNS *Neuroscience & Therapeutics* **15**:65-75 (2009).

Jensen B, Chen J, Furnish T, Wallace M. Medical marijuana and chronic pain: a review of basic science and clinical evidence. *Current Pain & Headache Reports* **19**:50 (2015).

Johannes CB, Le TK, Zhou X, Johnston JA, Dworkin RH. The prevalence of chronic pain in United States adults: results of an internet-based survey. *Journal of Pain* **11**:1230-1239 (2010).

Kahan M, Srivastava A, Spithoff S, Bromley L. Prescribing smoked cannabis for chronic noncancer pain. *Canadian Family Physician* **60**:1083-1090 (2014).

Kazantzis NP, Casey SL, Seow PW, Mitchell VA, Vaughan CW. Opioid and cannabinoid synergy in a mouse neuropathic pain model. *British Journal of Pharmacology*, **173**:2521-2531 (2016).

Koppel BS, Brust JCM, Fife T, Bronstein J, Youssof S, Gronseth G, Gloss D. Systematic review: efficacy and safety of medical marijuana in selected neurologic disorders: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* **82**:1556-1563 (2014).

Kozela E, Lev N, Kaushansky N, Eilam R, Rimmerman N, Levy R, Ben-Nun A, Juknat A, Vogel Z. Cannabidiol inhibits pathogenic T cells, decreases spinal microglial activation and ameliorates multiple sclerosis-like disease in C57BL/6 mice. *British Journal of Pharmacology* **163**:1507-19 (2011).

Kwiatkoski M, Guimarães FS, Del-Bel E. Cannabidiol-treated rats exhibited higher motor score after cryogenic spinal cord injury. *Neurotoxicology Research* **21**:271-80 (2012).

Lastres-Becker I, Molina-Hogado F, Ramos J, Mechoulam R, Fernández-Ruiz J. Cannabinoids provide neuroprotection against 6-hydroxydopamine toxicity in vivo and in vitro: relevance to Parkinson's disease. *Neurobiology of Disease* **19**:96-107 (2005).

Lee MC, Ploner M, Wiech K, Bingel U, Wanigasekera V, Brooks J, Menon DK, Tracey I. Amygdala activity contributes to the dissociative effect of cannabis on pain perception. *Pain* **154:**124-134 (2013).

Lerman I, Davis BA, Moeller Bertam T, Proudfoot J, Hauger RL, Coe, CL, Patel PM, Baker DG. Posttraumatic stress disorder influences the nociceptive and intrathecal cytokine response to a painful stimulus in combat veterans. *Psychoneuroendocrinology* **73**:99-108 (2016).

Lucas P, Walsh Z, Crosby K, Callaway R, Bell-Isle L, Kay R, Capler R, Holtzman S. Substituting cannabis for prescription drugs, alcohol and other substances among medical cannabis patients: the impact of contextual factors. *Drug and Alcohol Review* **35**:326-333 (2016).

Lynch ME, Cambell F. Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials. *British Journal of Clinical Pharmacology* **72**:735-744 (2011).

Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. *Nature* **346**:561-564 (1990).

McPartland JM, Duncan M, Di Marzo V, Pertwee RG. Are cannabidiol and Δ9-tetrahydrocannabivarin negative modulators of the endocannabinoid system? A systematic review. *British Journal of Pharmacology* **172**:737-753 (2015).

Mecha M, Carrillo-Salinas FJ, Feliú A, Mestre L, Guaza C. Microglia activation states and cannabinoid system: therapeutic implications. *Pharmacology & Therapeutics* **doi: 10.1016/j.pharmthera.2016.06.011** (2016).

Mechoulam R, Gaoni Y. A total synthesis of DL-delta-1-tetrahydrocannabinol, the active constituent of hashish. *Journal of the American Chemical Society* **87**:3273-3275 (1965).

Meier MH, Caspi A, Cerdá M, Hancox RJ, Harrington HL, Houts R, Poulton R, Ramrakha S, Thomson WM, Moffitt TE. Associations between cannabis use and physical health

problems in early midlife: a longitudinal comparison of persistent cannabis vs tobacco users. *JAMA Psychiatry* **73**:731-740 (2016).

Meng ID, Manning BH, Martin W, Fields HL. An analgesia circuit activated by cannabinoids. *Nature* **395**:381-383 (1998).

Mendoza Temple L. Medical marijuana and pain management. *Disease-a-Month* **doi:10.1016/j.disamonth.2016.05.014** (2016).

Oddi S, Latini L, Viscomi MT, Bisichhia E, Molinari M, Maccarrone M. Distinct regulation of nNOS and iNOS by CB2 receptor in remote delayed neurodegeneration. *Journal of Molecular Medicine* **90**:371-87 (2012).

Pacher P, Mackie K. Interplay of cannabinoid 2 (CB2) receptors with nitric oxide synthases, oxidative and nitrative stress, and cell death during remote neurodegeneration. *Journal of Molecular Medicine* **90**:247-51 (2012).

Pope C, Mechoulam R, Parsons L. Endocannabinoid signaling in neurotoxicity and neuroprotection. *Neurotoxicology* **31**:562-71 (2010).

Pradhan S, Andreasson K. Commentary: progressive inflammation as a contributing factor to early development of Parkinson's disease. *Experimental Neurology* **241**:148-55 (2013).

Pryce G, Ahmed Z, Hankey DJ, Jackson SJ, Croxford JL, Pocock JM, Ledent C, Petzold A, Thompson AJ, Giovannoni G, Cuzner ML, Baker D. Cannabinoids inhibit neurodegeneration in models of multiple sclerosis. *Brain* **126**:2191-202 (2003).

Ramirez SH, Haskó J, Skuba A, Fan S, Dykstra H, McCormick R, Reichenbach N, Krizbai I, Mahadevan A, Zhang M, Tuma R, Son Y-J, Persidsky Y. Activation of cannabinoid receptor 2 attenuates leukocyte-endothelial cell interactions and blood-brain barrier dysfunction under inflammatory conditions. *Journal of Neuroscience* **32**:4004-16 (2012).

Rom S, Zuluaga-Ramirez V, Dykstra H, Reichenbach NL, Pacher P, Persidsky Y. Selective activation of cannabinoid receptor 2 in leukocytes suppresses their engagement of the brain endothelium and protects the blood-brain barrier. *American Journal of Pathology* **183**:1-11; http://dx.doi.org/10/1016/j.ajpath.2013.07.033 (2013)

Rudd RA, Aleshire N, Zibbell JE, Gladden RM. Increases in drug and opioid overdose deaths – United States, 2000 – 2014. *MMWR* **64**:1378-1382 (2016).

Saito VM, Rezende RM, Teixeira AL. Cannabinoid modulation of neuroinflammatory disorders. *Current Neuropharmacology* **10**:159-66 (2012).

Scavone JL, Sterling RC, Van Bockstaele EJ. Cannabinoid and opioid interactions: implications for opiate dependence and withdrawal. *Neuroscience* **248**:637-654 (2013).

Scotter EL, Abood ME, Glass M. The endocannabinoid system as a target for the treatment of neurodegenerative disease. *British Journal of Pharmacology* **160**:480-98 (2010).

Skaper SD, Buriani A, Dal Toso R, Petrelli L, Romanello S, Facci L, Leon A. The ALIAmide palmitoylethanolamide and cannabinoids, but not anandamide, are protective in a delayed postglutamate paradigm of excitotoxic death in cerebellar granule neurons. *PNAS* **93**:3984-3989 (1996).

Skaper SD, Di Marzo V. Endocannabinoids in nervous system health and disease: the big picture in a nutshell. *Philosophical Transactions of The Royal Society B* **367**:3193-3200 (2012).

Touriño C, Zimmer A, Valverde O. THC prevents MDMA neurotoxicity in mice. *PLoS One* **5**:e9143 (2010).

van der Stelt M, Veldhuis WB, Bär PR, Veldink GA, Vliegenthart JF, Nicolay K. Neuroprotection by Deltag-tetrahydrocannabinol, the main active compound in marijuana, against ouabain-induced in vivo excitotoxicity. *Journal of Neuroscience* **21**:6475-9 (2001).

Wallace M, Schulteis G, Atkinson JH, Wolfson T, Lazzaretto D, Bentley H, Gouaux B, Abramson I. Dose-dependent effects of smoked cannabis on capsaicin-induced pain and hyperalgesia in healthy volunteers. *Anesthesiology* **107**:785-796 (2007).

Walters ET. Neuroinflammatory contributions to pain after SCI: roles of central glial mechanisms and nociceptor-mediated host defense. *Experimental Neurology* **258**:48-61 (2014).

Ware MA, Wang T, Shapiro S, Collet J-P for the COMPASS Study Team. Cannabis for the management of pain: assessment of safety study (COMPASS). *Journal of Pain* **16**:1233-1242 (2015).

Webb CW, Webb SM. Therapeutic benefits of cannabis: a patient survey. *Hawai'i Journal of Medicine & Public Health* **73**:109-11, 2014.

Whiting P, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, Keurentjes C, Lang S, Misso K, Ryder S, Schmidlkofer S, Westwood M, Kleijnen J. Cannabinoids for medical use: a systematic review and meta-analysis. *JAMA* **313**:2456-2473 (2015).

Wilsey B, Marcotte T, Tsodikov A, Millman J, Bentley H, Gouaux B, Fishman S. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. *Journal of Pain* **9**:506-521 (2008).

Wilsey B, Marcotte TD, Deutsch R, Gouaux B, Sakai S, Donaghe H. Low dose vaporized cannabis significantly improves neuropathic pain. *Journal of Pain* **14**:136-148 (2013).

Wilsey B, Marcotte TD, Deutsch R, Zhao H, Prasad H, Phan A. An exploratory human laboratory experiment evaluating vaporized cannabis in the treatment of neuropathic pain from spinal cord injury and disease. *Journal of Pain* doi: 10.1016/j.pain.2016.05.010 (2016).

Zheng G, Hong S Hayes JM, Wiley JW. Chronic stress and peripheral pain: evidence for distinct, region-specific changes in visceral and somatosensory pain regulatory pathways. *Experimental Neurology* **273**:301-311 (2015).

Zuardi AW. Cannabidiol: from an inactive cannabinoid to a drug with wide spectrum of action. *Revista Brasiliera Psiquiatria* **30**:271-80 (2008).