Send Orders for Reprints to reprints@benthamscience.net

402 *Current Neuropharmacology*, **2021**, *19*, **402-432**

SYSTEMATIC REVIEW ARTICLE

The Therapeutic Potential and Usage Patterns of Cannabinoids in People with Spinal Cord Injuries: A Systematic Review

Kylie J. Nabata[1,2,#], Emmanuel K. Tse[1,2,#], Tom E. Nightingale[1,3,4,#], Amanda H.X. Lee[1], Janice J. Eng[1,5,6,7], Matthew Querée[5,6,7], Matthias Walter[1,8] and Andrei V. Krassioukov[1,3,7,*]

[1]International Collaboration On Repair Discoveries (ICORD), University of British Columbia (UBC), Vancouver, Canada; [2]MD Undergraduate Program, Faculty of Medicine, UBC, Vancouver, Canada; [3]Department of Medicine, Division of Physical Medicine and Rehabilitation, UBC, Vancouver, Canada; [4]School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham, Birmingham, UK; [5]Department of Physical Therapy, UBC, Vancouver, Canada; [6]Spinal Cord Injury Research Evidence Team, Vancouver, Canada; [7]GF Strong Rehabilitation Centre, Vancouver Coastal Health, Vancouver, Canada; [8]Department of Neuro-Urology, Swiss Paraplegic Centre, Nottwil, Switzerland

Abstract: ***Background*:** People with spinal cord injuries (SCI) commonly experience pain and spasticity; limitations of current treatments have generated interest in cannabis as a possible therapy.

***Objectives*:** We conducted this systematic review to: 1) examine usage patterns and reasons for cannabinoid use, and 2) determine the treatment efficacy and safety of cannabinoid use in people with SCI.

***Methods*:** PubMed, Embase, Web of Science and Cumulative Index to Nursing and Allied Health Literature databases were queried for keywords related to SCI and cannabinoids.

***Results*:** 7,232 studies were screened, and 34 were included in this systematic review. Though 26 studies addressed cannabinoid usage, only 8 investigated its therapeutic potential on outcomes such as pain and spasticity. The most common method of use was smoking. Relief of pain, spasticity and recreation were the most common reasons for use. A statistically significant reduction of pain and spasticity was observed with cannabinoid use in 83% and 100% of experimental studies, respectively. However, on examination of randomized control trials (RCTs) alone, effect sizes ranged from -0.82 to 0.83 for pain and -0.95 to 0.09 for spasticity. Cannabinoid use was associated with fatigue and cognitive deficits.

***Conclusion*:** Current evidence suggests that cannabinoids may reduce pain and spasticity in people with SCI, but its effect magnitude and clinical significance are unclear. Existing information is lacking on optimal dosage, method of use, composition and concentration of compounds. Long-term, double-blind, RCTs, assessing a wider range of outcomes should be conducted to further understand the effects of cannabinoid use in people with SCI.

ARTICLE HISTORY

Received: February 10, 2020
Revised: March 12, 2020
Accepted: April 15, 2020

DOI:
10.2174/1570159X18666200420085712

Keywords: Spinal cord injury, cannabinoids, cannabis, marijuana, pain, spasticity.

1. INTRODUCTION

Spinal cord injury (SCI) is a life-long condition with deleterious effects on an individual's physical, mental and social wellbeing. Compared to the general population, people with SCI have a lower health-related quality of life due to a combination of poor physical health, stress, and secondary health conditions [1, 2]. In 2016, there were estimated one million new cases of SCI globally, with an incidence of 13 per 10, 000 individuals [3].

Following an SCI, people commonly suffer from spasticity and pain [4, 5]. In the SCI population, an estimated 65-78% of individuals report symptoms of spasticity, within the first year after injury [6, 7]. As many as 80% of people with SCI will experience neuropathic pain (NPP) [8]. Pain at the level of injury may consist of both peripheral and central NPP, while below-level pain is isolated central NPP [5]. It is also common for a person with SCI to experience difficulties performing activities of daily living, sleep disturbances, development of contractures, pressure ulcers, infections and a negative self-image [6]. These conditions are difficult to treat and interventions are often unsuccessful. The current anti-spastic and analgesic medications carry wide-ranging side-effect profiles and are costly [9, 10]. The inefficiency of

*Address correspondence to this author at the International Collaboration On Repair Discoveries (ICORD), University of British Columbia (UBC), Vancouver, Canada; E-mail: krassioukov@icord.org

[#]These authors contributed equally to this work.

1570-159X/21 $65.00+.00

the current treatment model has led people with SCI to explore alternative methods to manage spasticity and pain.

One such therapy recently garnering international attention is medicinal cannabis, currently legalized in Canada, 28 American states, the District of Columbia, Guam, and Puerto Rico [11, 12]. Public acceptance of cannabinoids for both medical and recreational purposes is increasing, with a recent survey reporting that two-thirds of medical cannabinoid users felt supported by friends and family [13].

1.1. Cannabinoids for Therapeutic Purposes

The human endocannabinoid system is comprised of cannabinoid receptors found throughout the central and peripheral nervous systems (CB1-Receptors) as well as the immune system (CB2-Receptors) [14]. Plants belonging to the genus *Cannabis* produce over 60 cannabinoid compounds, including the psychotropic cannabinoid Δ9-tetrahydrocannabinol (THC) and the non-psychoactive cannabidiol (CBD) [15]. THC binds to both the CB1- and CB2-Receptors with high affinity, while CBD shows little affinity for either receptor, but this may be overcome by increasing the dose [16]. These compounds mimic naturally occurring ligands at cannabinoid receptors in the human body to modulate physiological functions, and it is believed that their action on the central nervous system-located CB1-Receptors is what reduces spasticity [17]. THC and CBD can also influence other receptors, such as ion channels [18-24]. Preclinical studies have revealed that the analgesic effect of cannabinoids involves the inhibition of the release of neurotransmitters and neuropeptides from presynaptic nerve endings, modulation of postsynaptic neuron excitability, activation of descending inhibitory pain pathways and reduction of neural inflammation [25-28].

To date, the effects of cannabinoids have been studied in clinical trials to treat nausea and vomiting due to cancer chemotherapy, loss of appetite in people with HIV-induced or cancer-related weight loss, chronic pain, spasticity in people with multiple sclerosis (MS), intraocular pressure in people with glaucoma, and other conditions, such as SCI [29-34].

Despite the growing body of literature on medical cannabinoids, its use as a therapeutic alternative for SCI has not been thoroughly studied. Given the recent legalization of cannabinoids, its widespread usage, and prevalence of secondary conditions such as refractory pain and spasticity in people with SCI, it is necessary to conduct a rigorous review of the effects and therapeutic potential of cannabinoids. The purpose of this systematic review is to analyze the literature on the use of medical cannabinoids in people with SCI to answer the following: 1) characteristics of users, 2) patterns of use, 3) reasons for use, 4) therapeutic effects, and 5) associated side effects of cannabinoid use.

2. METHODS

2.1. Literature Search Strategy

A systematic review of all relevant literature, published from the database inception until February 29th, 2020, was conducted using four databases (PubMed, Embase, Web of Science and Cumulative Index to Nursing and Allied Health Literature (CINAHL)) and keywords for SCI and cannabis (Table **e-1**) in accordance with the Cochrane Handbook for Systematic Reviews of Interventions guidelines [35]. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to report our systematic review [36]. No protocol or registry entry is available for this systematic review.

2.2. Study Selection

Studies were included for qualitative analysis if they met the following criteria: (1) conducted with humans; (2) included at least two adults with an SCI; and (3) examined the effects of cannabinoids (in any preparation: synthetic or natural, form, or route of administration) against any comparison product. We included all study designs except case studies, reviews (*i.e.* narrative reviews, book chapters), opinion papers, non-peer-reviewed work, conference abstracts or papers and studies where the full text was unavailable. Studies were also excluded if the information on patient demographics, research design, intervention, and/or results could not be extracted accurately from the article. Non-randomized studies of interventions (NRSI) were included in the systematic review as recommended by the Cochrane handbook, which consider the inclusion of NRSI when RCTs are lacking [35].

2.3. Study Appraisal

Independent reviewers (author 1 and 2) screened titles, abstracts, and full-texts; only eligible studies were included in the qualitative analysis. A third reviewer (author 3) resolved discrepancies.

Fig. **1** illustrates the PRISMA flow diagram. A consensus was achieved (between authors 1-3) on data to be extracted from studies, which included author and year of study, study design, population characteristics (*e.g.*, etiology, level of and time since SCI), intervention, dosage and form of cannabinoid, outcomes measured, and side effects. Data extraction from observational and experimental studies was separated and performed independently by two authors. The principal summary measure was the difference in means.

Reviewers (author 1 and 2) also assessed observational studies (14-item checklist), pre-post trials (12-item checklist) and randomized control trials (RCTs) (14-item checklist) for

Table e-1. Search terms.

Search keywords for spinal cord injury	spinal cord OR spinal injur* OR SCI OR spinal cord damage OR spinal cord stroke OR spinal cord insult OR paraplegi* OR tetraplegi* OR quadriplegi*
Search keywords for cannabis	cannabis OR marijuana OR cannabinoid OR tetrahydrocannabinol OR THC OR cannabidiol OR CBD

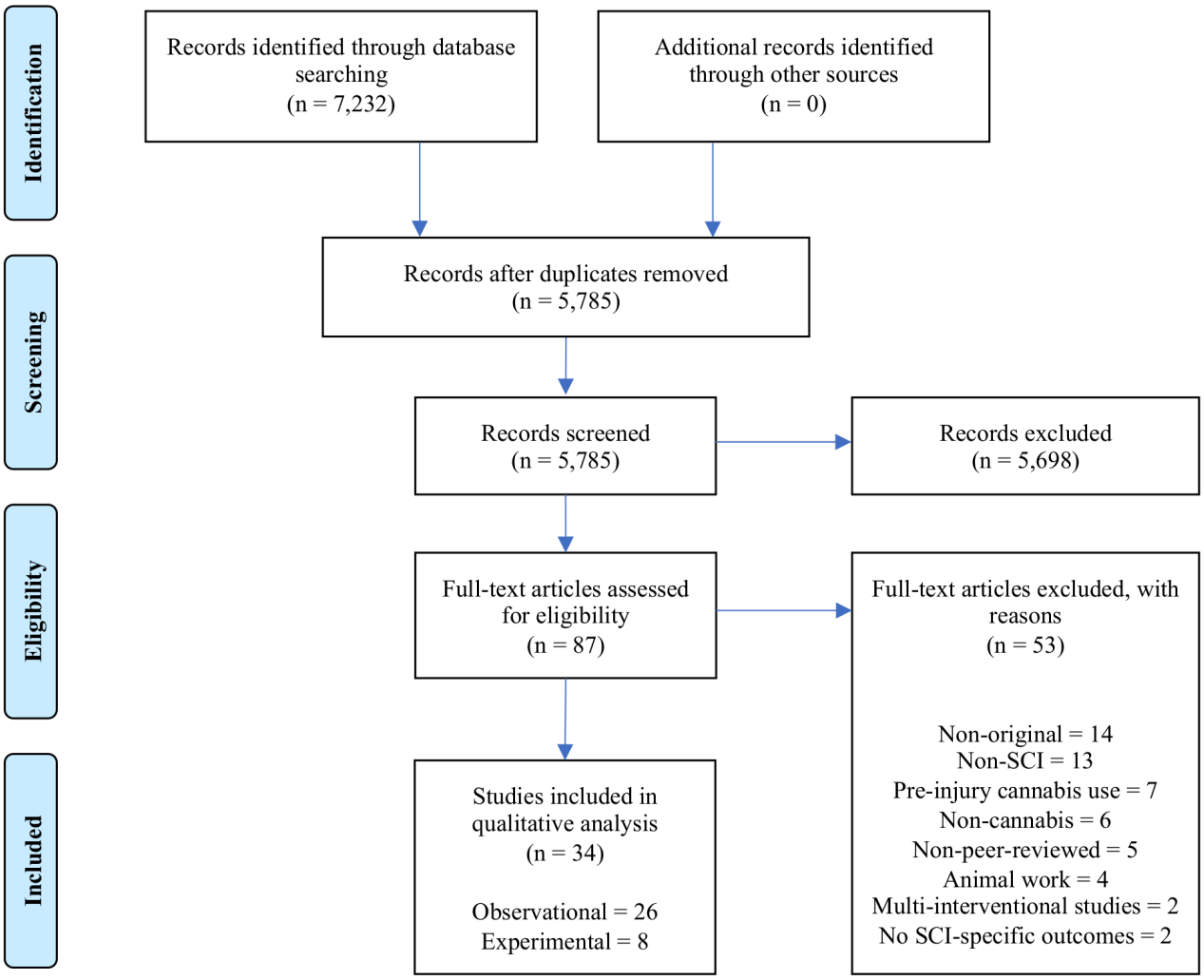

Fig. (1). PRISMA Flow Diagram.

methodologic quality and bias using the National Institute of Health (NIH) assessment tool [37].

2.4. Data Analysis

A modified coding system described by Sallis *et al*. [38], was used to summarise the studies reporting the effect of cannabinoids on various SCI-based outcomes. If 0-33% of the studies reported a statistically significant difference between cannabinoids and placebo, the result was coded as no effect (0). If 34-59% of the studies reported a statistically significant difference, the result was categorised as inconsistent (?). If 60-100% of the studies reported a statistically significant difference, the result was rated as positive (+) or negative (-). When four or more studies supported a difference or no difference, it was coded as ++, --, 00, respectively to indicate consistent observations. The code ?? indicated a marker that has been examined in four or more studies with inconsistent findings. Coding analysis was conducted on all primary and secondary outcomes measures.

For the RCTs, the effect size was calculated based on the standardized mean difference [39]. Effect sizes were calculated for pain and spasticity because they are commonly experienced by individuals with SCI and have been studied with cannabis in other conditions such as chronic non-cancer pain and spasticity for MS [31, 40]. Effect sizes of NRSI were not calculated. These study designs substantially inflate the effect magnitude compared to control group designs, as the control group captures any non-intervention influences, for example, familiarization to the outcome measure [41].

3. RESULTS

PubMed, Embase, Web of Knowledge, CINAHL and searches yielded 7,232 citations. In total, 34 publications were eligible and included (Fig. **1**, Table **e-2**).

3.1. Description of Studies

Of the 34 studies included in this systematic review, 26 were observational and 8 were experimental. The results were grouped based on the objectives: 1) characteristics of users, 2) patterns of use, 3) reasons for use, 4) therapeutic effects of cannabinoids, and 5) side effects associated with cannabinoid use. Homogenous SCI participant populations were included in 18 out of the 22 observational studies and 4

of the 8 experimental studies. From the experimental studies, Dronabinol capsules were used in two studies, at different doses, while the other studies used variable proportions of CBD and THC as their interventions. Placebo was the most common comparator, used in six of the eight studies.

3.2. Quality of Studies

Among the observational studies, 19 were of poor quality and seven of fair quality (Table **e-3**). Of the seven RCTs, one study provided good evidence, four studies provided fair quality evidence and two were poor quality studies (Table **e-4**), while the single pre-/post-study was evaluated as poor quality (Table **e-5**).

3.3. Aim 1: Characteristics of Cannabinoid Users

Cannabinoid users were found to be younger [42-44] compared to non-users. A Danish study (n=537) by Andresen *et al.* [44], reported a mean age of 42.5 years for current users (over the last 2 years) as compared to 55.8 years for non-users. Cannabinoid users were also more likely to be single [44, 45] compared to non-users. Six studies demonstrated no significant difference in cannabinoid use between males and females [42, 44-48]. The results of two cross-sectional surveys by Hwang *et al.* [48], and Young *et al.* [43], suggested that low education status was associated with greater cannabinoid use, but this was not supported by other studies; Drossel *et al,* [45], and Hawley *et al.* [49]. Across studies reporting participants' demographics, no major differences were found between users and non-users in terms of their socioeconomic status, social support or medical complications [42-43, 48].

3.4. Aim 2: Patterns of Cannabinoid Use

The results of three studies examining the frequency (monthly, weekly, daily) of cannabinoid use in people with SCI were inconsistent, as two studies (n=244, n=215) reported a larger percentage of daily users [45, 48], while one large study (n=1,619) demonstrated a higher proportion of monthly users (Table **1**) [47]. Three studies reported the most common routes of administration. All studies ranked smoking as the most frequently used, followed by edibles and vapor in two studies (n=244, n=116) [45, 49], and the converse order in one smaller study (n=30) [50]. In general, inhalation (smoking, vaping) was more common than ingestible (oil, drops, food) administration [51, 52]. Other medications that were not SCI-specific were often used in combination with cannabinoids [46, 50].

3.5. Aim 3: Reasons for Cannabinoid Use

Table **2** summarizes the variety of reasons for cannabinoid use. Relief of pain, spasticity and recreation were typically the top three responses [44, 45, 49, 50, 53, 54].

3.6. Aim 4: Treatment Efficacy of Cannabinoids

3.6.1. Pain

Six experimental studies, including a total of ten therapeutic intervention-arms, reported data related to a range of cannabinoids (Dronabinol; 1',1'-dimethylheptyl-Δ^8-tetrahydrocannabinol-11-oic acid (CT-3); THC cigarettes; CBD-/THC-rich sublingual spray; THC vaporized cannabinoid) for the treatment of pain in people with SCI (Table **3**, Table **e-6**) [55-60]. Four of these studies reported pain outcomes using a visual analogue scale (VAS), a measure of pain subjectively rated on a continuum from none to an extreme amount of pain, with clinically meaningful changes in chronic pain estimated as a decrease by 2.3 points and 30-mm on the 11-point and 100-mm scales, respectively [56, 58-62]. The single study rated good-quality by Karst *et al.* [56], concluded that CT-3 significantly ($p=0.02$) reduced pain compared to placebo at three hours after oral administration. Three fair-quality RCTs investigated the analgesic effects of cannabinoids and showed that cigarettes (containing 3.5% and 6.9% THC), vaporized THC (2.9% and 6.7%) and CBD-rich or THC-rich sublingual sprays significantly ($p<0.05$) reduced pain compared to placebo [58-60]. Two of these studies concluded that cannabinoids significantly improved the following multidimensional pain descriptors associated with NPP: intensity, sharpness, burning, aching, sensitivity, unpleasantness, deep pain, superficial pain. Neither study found any improvement in allodynia [59, 60]. A poor-quality study found that oral Dronabinol had no significant analgesic effects compared to placebo [57]. However, an open-label pre-/post-study investigating oral Dronabinol concluded a significant decrease in pain ($p=0.047$) compared to baseline after one day, although this significant decrease did not persist in later follow-ups at 8 and 43 days [55]. None of the studies that investigated pain using a VAS reported clinically meaningful differences [56, 58, 60]. Overall, the effect sizes of cannabinoids on pain as studied in the RCTs (n=5) ranged from -0.82 to 0.83. A statistically significant improvement in pain was reported in 83% of all experimental studies (n=6) (Table **e-6**, Table **e-7**, Fig. **2**).

Six observational studies assessed the analgesic effects of cannabinoids alone (Table **4**). A small study (n=10) reported

Table e-2. Database search results.

Database	Date Accessed	Results Returned
PubMed	February 29, 2020	3968
Embase	February 29, 2020	2168
Web of Knowledge	February 29, 2020	981
Cumulative Index to Nursing and Allied Health Literature	February 29, 2020	115

Table e-3. Quality of the observational studies.

Author, Year	Research Question/ Objective Clearly Stated?	Study Population Specified and Defined?	Participation Rate of Eligible Persons ≥50%?	Subjects from Same/Similar Populations? Inclusion/ Exclusion Criteria Prespecified and Applied Uniformly?	Sample Size Justification, Power Description, Variance and Effect Estimates Provided?	Exposure(s) Measured Prior to the Outcome(s) Measured?	Sufficient Timeframe for Association between Exposure and Outcome to be Seen?	Did the Study Examine Different Levels of the Exposure as Related to the Outcomes?	Exposure Measures Defined, Valid, Reliable and Implemented Consistently?	Exposure(s) Assessed more than Once Over Time?	Were Outcomes Assessed Reliable and Consistent?	Were Assessors Blinded to Exposure Status of Participants?	Was Loss to Follow-up after Baseline ≤20%?	Key Potential Confounding Variables Measured and Adjusted Statistically for their Impact on Relationship between Exposure(s) and Outcome(s)?	Overall Quality
Dunn & Davis, 1974 [63]	+	-	?	+	-	-	-	-	+	-	-	N/A	N/A	-	POOR
Malec *et al*., 1982 [64]	+	-	+	+	-	-	-	-	+	-	+	N/A	N/A	-	POOR
Heinemann *et al*., 1991 [65]	+	-	+	+	-	N/A	+	-	-	+	+	N/A	+	+	POOR
Rothstein *et al*., 1992 [66]	+	-	?	+	-	-	-	+	+	N/A	+	N/A	N/A	-	POOR
Young *et al*., 1995 [43]	+	-	-	+	-	-	-	+	+	-	+	N/A	N/A	+	POOR
Kolakowsky-Hayer *et al*., 2002 [67]	+	+	?	+	-	-	-	+	+	-	+	N/A	N/A	+	FAIR
Warms *et al*., 2002 [68]	+	+	+	+	-	-	-	-	+	-	+	N/A	N/A	-	POOR
Grotenhermen & Schnelle, 2003 [51]	+	-	?	+	-	-	-	+	+	-	+	N/A	N/A	-	POOR
Gorter, 2005 [52]	+	-	-	+	-	-	-	+	+	-	-	N/A	N/A	-	POOR
Cardenas & Jensens, 2006 [53]	+	+	+	+	-	-	-	+	+	-	-	N/A	N/A	-	POOR
Mahoney *et al*., 2007 [69]	+	-	+	+	N/A	-	-	-	+	-	+	N/A	N/A	N/A	POOR
Aggarwal *et al*., 2009 [46]	+	-	+	+	-	-	?	-	+	N/A	-	N/A	N/A	N/A	POOR
Heutink *et al*., 2011 [70]	+	+	+	+	-	-	-	+	+	-	+	N/A	N/A	-	POOR
Hwang *et al*., 2012 [48]	+	-	?	+	-	-	-	+	+	-	+	N/A	N/A	+	FAIR
Fekete *et al*., 2015 [42]	+	+	+	+	-	-	-	+	+	-	+	N/A	N/A	+	FAIR
Shroff, 2015 [54]	+	-	?	+	N/A	-	-	-	+	-	+	N/A	N/A	N/A	POOR

(Table e-3) contd….

Author, Year	Research Question/ Objective Clearly Stated?	Study Population Specified and Defined?	Participation Rate of Eligible Persons ≥50%?	Subjects from Same/Similar Populations? Inclusion/ Exclusion Criteria Prespecified and Applied Uniformly?	Sample Size Justification, Power Description, Variance and Effect Estimates Provided?	Exposure(s) Measured Prior to the Outcome(s) Measured?	Sufficient Timeframe for Association between Exposure and Outcome to be Seen?	Did the Study Examine Different Levels of the Exposure as Related to the Outcomes?	Exposure Measures Defined, Valid, Reliable and Implemented Consistently?	Exposure(s) Assessed more than Once Over Time?	Were Outcomes Assessed Reliable and Consistent?	Were Assessors Blinded to Exposure Status of Participants?	Was Loss to Follow-up after Baseline ≤20%?	Key Potential Confounding Variables Measured and Adjusted Statistically for their Impact on Relationship between Exposure(s) and Outcome(s)?	Overall Quality
Drossel *et al*., 2016 [45]	+	-	+	+	-	-	-	+	+	-	+	N/A	N/A	-	POOR
Andresen *et al*., 2017 [44]	+	+	+	+	-	-	-	+	+	-	+	N/A	N/A	+	FAIR
Clark *et al*., 2017 [47]	+	+	+	+	-	-	-	+	+	-	+	N/A	N/A	+	FAIR
Patel *et al*., 2017 [71]	+	-	+	+	-	-	?	-	+	N/A	+	N/A	N/A	-	FAIR
Bruce *et al*., 2018 [50]	+	-	+	+	-	-	-	+	+	-	+	N/A	N/A	N/A	POOR
Hawley *et al*., 2018 [49]	+	-	?	+	-	-	-	+	+	-	+	N/A	N/A	-	POOR
Bourke *et al*., 2019 [72]	+	-	?	+	N/A	-	-	-	+	-	+	N/A	N/A	N/A	POOR
Eldridge *et al*., 2019 [73]	+	-	-	+	-	-	?	-	+	-	+	N/A	N/A	-	POOR
Graupensperger *et al*., 2019 [74]	+	-	+	+	-	-	?	-	+	-	+	N/A	N/A	+	FAIR
Stillman *et al*., 2019 [75]	+	-	-	+	-	-	-	+	+	-	+	N/A	N/A	-	POOR

Note: N/A: not applicable, for study designs where the question could not be applied; ?: cannot be determined; +: yes; -: no.

that 50% of participants experienced a decrease in headache pain and 40% in phantom pain with cannabinoid use [63]. Another trial by Andresen *et al.* [44], described that among participants who used cannabinoids for pain, 59% of individuals reported good (35%) or very good (24%) efficacy for pain relief, while Warms *et al.* [68], reported an average of 4.25 on a 5-point scale for cannabinoid pain relief. Moreover, participants in the study by Cardenas & Jensen [53] self-reported mean pain relief of 6.62 out of 10 points, with relief typically lasting several hours (for 80% of participants). Participants in two survey studies, by Cardenas & Jensen [53] and Warms *et al*. [68], reported that cannabinoids were the most effective analgesic out of a total of 26 and 27 pain treatments, respectively. Both studies showed that cannabinoids provided substantially more pain relief than non-steroidal anti-inflammatory drugs, baclofen, tricyclic antidepressants, and acetaminophen, among many other treatments [53, 68]. In a retrospective chart review of pain clinic patients by Aggarwal *et al*. [46], medical cannabinoids were the most effective treatment in 19% of patients. Five studies, including three interview-based studies also reported that cannabis was preferred over prescribed medications due to fewer side effects, including less dehydration, memory loss and drowsiness [46, 50, 54, 72]. Overall, cannabinoids were subjectively rated as the most effective pain relief treatment across several studies [44, 46, 50, 53, 68].

3.6.2. Spasticity

Five experimental studies, including a total of ten therapeutic intervention arms, investigated the benefits of cannabinoids on spasticity in people with SCI (Table **5**, Table **e-6**) [55, 58, 60, 76, 77]. The Ashworth Scale (AS) (n=3) [55, 58, 77], pendulum drop test (n=2) [76, 77], spasticity numerical rating scale (NRS) (n=2) [58, 77] and the patients' self-ratings of spasticity (severity point scales) (n=3) [55, 58, 60] were the most commonly used measures of spasticity. One study used the Modified Ashworth Scale (MAS) [55]. It is worth noting that clinically meaningful changes in spasticity measured by the MAS have been estimated to be a decrease by more than 1-point [78, 79].

Table e-4. Quality of the randomized control trial studies.

Author, Year	Randomization?	Adequate Method of Randomization?	Concealed Treatment Allocation?	Participants and Providers Blinded to Group Assignment?	Assessors Blinded to Group Assignment?	Groups Similar at Baseline?	Overall Drop-out Rate <20% at Endpoint?	Differential Drop-out Rate <15% at Endpoint?	High Adherence to Intervention?	Other Interventions Avoided or Similar in Groups?	Were Outcomes Assessed Reliable and Consistent?	Was Sample Size Sufficiently Large to Detect a Difference in Main Outcome with ≥80% Power?	Were Outcomes Reported or Subgroups Prespecified?	Participants Analyzed to Group they were Originally Assigned?	Overall Quality
Karst *et al*., 2003 [56]	+	+	+	+	+	-	+	+	+	+	+	+	+	+	GOOD
Wade *et al*., 2003 [58]	+	+	+	+	+	N/A	+	N/A	?	-	+	+	+	+	FAIR
Hagenbach *et al*., 2007 [55]	+	?	+	+	?	+	+	+	+	+	+	-	+	+	FAIR
Wilsey *et al*., 2008 [59]	+	+	+	+	+	+	+	+	-	+	+	-	+	+	FAIR
Rintala *et al*., 2010 [57]	+	+	+	+	+	+	-	?	+	+	+	-	+	+	POOR
Pooyania *et al*., 2010 [77]	+	+	+	+	?	-	+	+	+	-	+	-	+	+	POOR
Wilsey *et al*., 2016 [60]	+	+	+	+	?	+	+	+	+	-	+	-	+	+	FAIR

N/A: not applicable, for study designs where the question could not be applied; ?: cannot be determined; +: yes; -: no.
A study was automatically considered poor quality with a significant risk of bias if it included a "fatal flaw". Examples of fatal flaws included high dropout rates, high differential dropout rates, no intention-to-treat analysis, or other unsuitable statistical analysis (*e.g*., completers-only analysis).

Table e-5. Quality of the pre-/post-studies.

Author, Year	Clearly Stated Study Question?	Clearly Described Eligibility/ Selection Criteria for Study Population?	Were Participants Representative of the Clinical Population of Interest?	Were all Eligible Participants that Met the Prespecified Entry Criteria Enrolled?	Was the Sample Size Sufficiently Large?	Was the Intervention Clearly Described and Delivered Consistently Across the Study Population?	Were the Outcomes Measures Prespecified, Clearly Defined, Valid, Reliable, and Assessed Consistently?	Were the People Assessing the Outcomes Blinded to the Participants' Exposures/Interventions?	Was the Loss to Follow-up after Baseline 20% of Less?	Did Statistical Methods Examine Changes in Outcome Measures from before to after Intervention? Did they Provide p-values?	Were Outcome Measures of Interest Taken Multiple Times before the Intervention and Multiple Times after the Intervention?	If the Intervention was Conducted at Group Level, did Statistical Analysis Take into Account the Use of Individual-level Data to Determine Effect at Group Level? Assigned?	Overall Quality
Kogel *et al*., 1995 [76]	+	+	+	NR	-	+	+	-	+	+/-	+	N/A	POOR

N/A: not applicable, for study designs where the question could not be applied; NR: not reported; +: yes; -: no.

Three fair-quality RCTs found cannabinoids to be effective in improving spasticity in people with SCI [55, 58, 60].

Wade *et al*. [58], determined that sublingual CBD, THC and 1:1 CBD:THC significantly reduced VAS scores ($p<0.05$) at 2 weeks. Oral Dronabinol reduced self-ratings of spasticity on day 1 ($p=0.033$) [55]. Wilsey *et al*. [60], found that 2.8% vaporized THC improved spasticity scales significantly compared to placebo ($p<0.0001$), while 6.7% vaporized THC did not. The single poor-quality study found that nabilone resulted in a significant reduction for those who exhibited the most spasticity, as measured by the total AS score [77]. However, the treatment group had higher spasticity at baseline. The pre-/post-studies determined that oral Dronabinol and rectal THC both improved spasticity [55, 76]. The one study that utilized the MAS demonstrated a clinically meaningful decrease in spasticity [55]. Among the RCTs (n=4), the effect size of cannabinoid use on spasticity ranged from -0.95 to 0.09; across all experimental studies, 100% of studies showed a statistically significant improvement in spasticity (n=5) (Table **e-6**, Table **e-7,** Fig. **2**).

Four observational studies investigated the therapeutic effect of cannabinoids on spasticity (Table **4**) [44, 63-64, 69]. Dunn and Davis [63] found that 50% of participants

Table 1. Patterns of cannabinoid use from observational studies.

Author, Year	Study Type	Legalization (Location)	Number of Participants (SCI/Total)	Inclusion Criteria	Exclusion Criteria	Male/Female/ Transgender	Mean Age	Tetraplegia/ Paraplegia/ Unknown	Mean Time Since Injury	Prevalence
Dunn & Davis, 1974 [63]	Cross-sectional	Illegal (Florida, USA)	10/10	SCI patients using cannabis	-	10/0/0	NR	NR	NR	N/A- cannabis use was inclusion criteria
Malec *et al*., 1982 [64]	Cross-sectional	Illegal (Wisconsin, USA)	43/43	SCI patients	-	38/5/0	NR	NR	NR	Within last yr: 56%
Heinemann *et al*., 1991 [65]	Case-series	Illegal (Illinois, USA)	86/86	13-66 age, 2+ yr since tSCI, English language, no cognitive impair-ment	-	59/27/0	39.5 (13-65)	47/39	13.1 ± 10.2	6 mo pre-SCI: 31%; Post-SCI: 42%
Rothstein *et al*., 1992 [66]	Cross-sectional	MC legal (New York, USA)	153/153	Male veterans with SCI	-	153/0/0	53 ± 1 (20-76)	NR	NR	Current (urinary cannabinoid test): 10%
Young *et al*., 1995 [43]	Cross-sectional	Illegal (Texas, USA)	123/123	17+ age, 9+ mo since tSCI, residu-al motor disability with assistive walking device if ambulatory	-	82/41/0	36 ± 10.9 (19-76)	Complete tetra: 53, complete para: 53, incom-plete: 17	9.7 ± 6.6	Current (regular basis at time of study): 16%
Kolakowsky-Hayner *et al*., 2002 [67]	Cross-sectional	Illegal (Virgin-ia, USA)	30/60	SCI and brain injury patients treated in trauma centre	-	56/4/0	35.0 ± 10.85	NR	1.4	Past 6-12 mo: 50% among illicit drug users (n=6 SCI, n=1 TBI)
Warms *et al*., 2002 [68]	Cross-sectional	MC legal starting Nov 1998, study V1 Feb 1997 – Jul 1998, V2 Aug 1998 – June 2000 (Washing-ton, USA)	471/471	18+ age, 6+ mo since SCI	-	334/137/0	42.5 ± 13.2 (18-84)	240/221, unknown: 9	NR	Ever: 3%
Grotenhermen & Schnelle[a], 2003 [51]	Cross-sectional	Dronabinol prescription and Δ9-THC special permit (Germany) and permit (Switzerland)	4/165	Members of Association for Cannabis as Medicine	No severe disease	101/64/0	Median age: 40.3 ± 12.4 (16-87)	NR	NR	Ever: 87%
Gorter[a], 2005 [52]	Cross-sectional	MC legal (Netherlands)	?/107	Members of Multiple Sclerosis society	-	48/59/0	Median age: 58.0	NR	NR	N/A- MC was inclusion criteria
Cardenas & Jensen, 2006 [53]	Cross-sectional	MC legal (Washington, USA)	117/117	18+ age, tSCI, chronic pain	Incomplete question-naires	85/32/0	48.8 ± 11.7 (21-79)	56/61	17.3 ± 10.9	Ever: 32%; Current: 20%
Mahoney *et al*., 2007 [69]	Interview	Illegal (Texas, USA)	24/24	1+ yr since SCI, spasticity, English language	-	17/7/0	45.1 (21-68)	13/11	16	NR
Aggarwal *et al*[a]., 2009 [46]	Retro-spective chart review	MC legal (Washington, USA)	5/139	18+ age, pain clinic patients, access to MC with valid doctor documentation	Cannabinoid receptor 1 blocker drug rimonabant	88/51/0	Median age: 48 (18-84)	NR	NR	N/A- MC was inclusion criteria

(Table 1) contd….

Author, Year	Study Type	Legalization (Location)	Number of Participants (SCI/Total)	Inclusion Criteria	Exclusion Criteria	Male/ Female/ Transgender	Mean Age	Tetraplegia/ Paraplegia/ Unknown	Mean Time Since Injury	Prevalence
Heutink *et al*., 2011 [70]	Cross-sectional	MC legal starting 2003, study 1990-2005 (the Netherlands)	279/279	18+ age, SCI rehab patients, living in community	-	173/106/0	51.3 ± 14.0 (25-81)	103/165, unknown: 11	11.6 ± 10.7	Past, discontinued: 6%; Current (at study): 3%
Hwang *et al*., 2012 [48]	Cross-sectional	Illegal (Florida, USA)	215/215	SCI before age 19, current age 21-25, former hospital patient	-	127/88/0	23.4 ± 0.9	112/101, unknown: 2	10.2 ± 4.9	Current (at least mo): 11%
Fekete *et al*., 2015 [42]	Cross-sectional	MC permit (Switzerland)	511/511	16+ age, tSCI or non-tSCI;	New SCI with palliative care, neurodegenerative diseases or Guillain-Barre syndrome; congenital conditions leading to SCI	373/138/0	52.9 ± 14.8	158/353	17.6 ± 13.0	Current (last 30 d): 7%
Shroff, 2015 [54]	Interview	MC legal (Canada)	53/53	19-65 age, 1+ years since SCI, BC resident, member of paraplegic association	-	42/11/0	NR	NR	NR	NR
Drossel *et al*., 2016 [45]	Cross-sectional	MC legal (Michigan & California, USA)	244/244	18+ age, 5+ years since tSCI, English language, neurogenic bowel and/or bladder, no cognitive limitations	-	181/63/0	49.7	134/110	18.6	Ever: 23%
Andresen *et al*., 2017 [44]	Cross-sectional	MC legal starting 2011, study 1990-2012 (Denmark)	537/537	Inclusion: 18+ age, acquired tSCI, rehab clinic patients	Incomplete questionnaires	413/124/0	54.6 ± 14.6 (18-88)	247/263, unknown: 27	18.2 ± 12.8	Ever: 36%; Current (last 2 yrs): 9%
Clark *et al*., 2017 [47]	Cross-sectional	MC illegal (Georgia & South Carolina, USA)	1619/1619	18+ age, 1+ year since tSCI, some residual impairment	No painful condition, no prescription pain med	1166/453/0	49.3 ± 14.2	453/1166	11.5 ± 9.2	Current (mo): 16%
Patel *et al*., 2017 [71]	Retrospective chart review	MC legal (Canada)	19/19	Patients of mobility clinic with documented SCI	-	14/5/0	46.7 (18-89)	NR	NR	Current: 16%
Bruce *et al*.[a], 2018 [50]	Interview	MC legal (Illinois, USA)	6/30	18+ age, smoked MC in past 3 mo, qualifying health condition for MC	-	19/11/0	44.6 ± 15.9	NR	NR	N/A- MC was inclusion criteria
Hawley *et al*., 2018 [49]	Cross-sectional	MC and recreational legal (Colorado, USA)	51/116	SCI rehab patient	-	95/21/0	47.1 ± 13.8 (22-74)	Tetra ABC: 38, para ABC: 31, tetra/para D: 41, unknown: 5	13.0	Before injury: 67%; After injury: 53%
Bourke *et al*., 2019 [72]	Interview	Illegal (New Zealand)	8/8	18+ age, SCI patients using cannabis for pain, residing in New Zealand, English speaking,	Comorbid conditions inhibiting communication and participation in interview	6/2/0	Age 20-39: n = 1, 40-59: n= 5, 60+: n=2	Tetra: 6 Para: 2	NR	N/A- MC was inclusion criteria

(Table 1) contd….

Author, Year	Study Type	Legalization (Location)	Number of Participants (SCI/Total)	Inclusion Criteria	Exclusion Criteria	Male/ Female/ Transgender	Mean Age	Tetraplegia/ Paraplegia/ Unknown	Mean Time Since Injury	Prevalence
Eldridge *et al*., 2019 [73]	Retro-spective chart review	Illegal (Indiana, USA)	20/20	18+ age, SCI patients received medical care at Eskenazi Medical Center	-	17/3/0	45.05 ± 13.84	NR	NR	Before injury: 25%
Graupen-sperger *et al*., 2019 [74]	Retro-spective chart review	MC legal starting 2016 and imple-mented Feb 2018, study Jan 1997-April 2018 (Penn-sylvania, USA)	6192/1466985	16+ age, patients at Penn State Hershey Medical Center	-	3368/2824/0	NR	NR	NR	Cannabis use disorder with SCI: 1% vs. non-SCI 0.2%
Stillman *et al*., 2019 [75]	Cross-sectional	39 states in USA, not disclosed; mixed legality	353/353	SCI patients included in mailing lists maintained by Thomas Jefferson University, University of Washington at Seattle, and Uni- versity of Alabama at Birmingham	-	183/107/3	52.74 (19-82)	NR	17.49	Current: 39% Past: 15%

Abbreviations: d: days; freq: frequency; MC: medical cannabis; mo: monthly; N/A: not applicable; NR: not reported; qd: daily; SCI: spinal cord injury; TBI: traumatic brain injury; THC: tetrahydrocannabinol; tSCI: traumatic spinal cord injury, wk: weekly; yr: yearly. [a]data listed not limited to people with SCI.

experienced a decrease in spasticity, while Malec *et al*. [64], concluded that 88% of participants self-reported mild (46%) to moderate (4%) reduction in spasticity, or complete elimination (38%) when graded on a 5-point scale (not present, mild, moderate, severe, very severe). Andresen *et al*. [44], examined the efficacy of cannabinoids in decreasing spasticity, with 59% of respondents describing a good (32%) or very good (27%) effect. Furthermore, participants in open-ended interviews conducted by Mahoney *et al*. [69], reported benefits in preventing, modulating and even stopping spasms.

3.6.3. Quality of Life and Daily Function

Mood, pain, and spasticity have been demonstrated to negatively impact activities of daily living, mobility and general health [44]. Overall, two studies [55, 58], comprised of five therapeutic intervention arms, reported the impact of cannabinoids on functional independence measures (Barthel Activities of Daily Living Index, Rivermead Mobility Index, General Health Questionnaire 28, Functional Independence Measure) and found that cannabinoids had no statistically significant effect (Table **6**, Table **e-6**) [55, 58]. On the contrary, one interview-based study reported that the analgesic properties of cannabis use could improve the quality of life due to functional improvement [72].

3.6.4. Cannabinoids and Opioids

Four observational studies compared the efficacy and safety profile of cannabinoids with opioids [46, 50, 53, 68]. Cannabinoids were noted to provide greater pain relief than all other pain medications, including opioids, such as codeine, methadone, oxycodone, Percodan, Percocet, and Vicodin. In particular, participants of semi-structured interviews reported quicker onset, longer duration of action, greater symptom relief and fewer side effects for cannabinoids compared to opioids, when prescribed for chronic conditions (*e.g*. rheumatoid arthritis, SCI, fibromyalgia) [50]. These findings were corroborated by two previously described cross-sectional studies that reported analgesic superiority of cannabinoids among people with SCI, including greater pain relief than opioids; however, no statistical analyses were conducted [53, 68].

Many participants reported fewer side effects of cannabinoids compared with opioid use (*i.e*. constipation, nausea, incapacitation and allergies) [46, 50, 54]. Opioids were also least likely to be continued as pain medication [53]. Finally, patients perceived cannabinoids as a means of harm reduction with respect to the addictive potential of opioids. Patients described using cannabinoids either alternatively or in conjunction with opioids reduced their opioid dose and dependence [46, 50].

3.7. Aim 5: Side Effects Associated with Cannabinoid Use

The specific side effects of cannabinoids varied between the experimental studies, but were not uncommon (Table **7**). Dry mouth, fatigue and increased hunger were the most commonly noted and were associated with both CBD and THC therapy [55-58]. Most of these side effects were rated as mild (dry mouth, drowsiness, itchiness, weakness, dizziness, confusion, incoordination, rash). However, a substantial number of side effects were reported as moderate (scale of mild, moderate and severe), such as constipation, fatigue and abdominal discomfort [57].

3.7.1. Cognition

Six experimental studies, comprised of ten therapeutic intervention arms, investigated the effect of cannabinoids on cognition in people with SCI, as secondary outcomes (Table **6**, Table **e-6**) [55-56, 58-60, 76]. Wade *et al*. [58], assessed cognition using the short orientation-memory-concentration test (SOMC), a measure of concentration. They found that

Table 2. Reasons for cannabinoid use from observational studies.

Author, Year	Study Type	Legalization (Location)	Number of Participants (SCI/Total)	Inclusion Criteria	Exclusion Criteria	Male/ Female	Mean Age	Tetraplegia/ Paraplegia/ Unknown	Mean Time Since Injury	Reasons for Use
Cardenas & Jensen, 2006 [53]	Cross-sectional	MC legal (Washington, USA)	117/117	18+ age, tSCI, chronic pain	Incomplete questionnaires	85/32	48.8 ± 11.7 (21-79)	56/61	17.3 ± 10.9	Chronic pain
Shroff, 2015 [54]	Interview	MC legal (Canada)	53/53	19-65 age, 1+ years since SCI, BC resident, member of paraplegic association	-	42/11	NR	NR	NR	Pain, spasm relief, relaxation, recreation
Drossel *et al*., 2016 [45]	Cross-sectional	MC legal (Michigan & California, USA)	244/244	18+ age, 5+ years since tSCI, English language, neurogenic bowel and/or bladder, no cognitive limitations	-	181/63	49.7	134/110	18.6	Pain relief 70%, spasticity 46%, anxiety 30%, bowel 11%, recreation 9%, bladder: 6%
Andresen *et al*., 2017 [44]	Cross-sectional	MC legal starting 2011, study 1990-2012 (Denmark)	537/537	Inclusion: 18+ age, acquired tSCI, rehab clinic patients	Incomplete questionnaires	413/124	54.6 ± 14.6 (18-88)	247/263, unknown: 27	18.2 ± 12.8	First use: pleasure 89%; SCI medicinal: pain and/or spasticity 22%; Current use: pleasure 63%, pain 60%, party 48%, spasticity 46%, depression 31%, sleep 29%, anxiety/stress 29%, fatigue 15%, appetite 15%, weakness 13%
Bruce *et al*[a]., 2018 [50]	Interview	MC legal (Illinois, USA)	6/30	18+ age, smoked MC in past 3 mo, qualifying health condition for MC	-	19/11	44.6 ± 15.9	NR	NR	Medicinal cannabis use with prescription meds: alternative 60%, tapering 27%, complementary 20%
Hawley *et al*., 2018 [49]	Cross-sectional	MC and recreational legal (Colorado, USA)	51/116	SCI rehab patient	-	95/21	47.1 ± 13.8 (22-74)	Tetra ABC: 38, para ABC: 31, tetra/para D: 41, unknown: 5	13.0	Spasticity 70%, recreation 63%, sleep 63%, pain 59%, decrease meds 52%, nausea 33%, appetite 33%, depression 33%

Abbreviations: ABCD: American Spinal Injury Association classification A (complete injury), B (incomplete – sensory is preserved), C (incomplete – most muscle groups below the level of injury have strength <3), D (incomplete– most muscle groups below the level of injury have strength >3); BC: British Columbia; MC: medical cannabis; NR: not reported; SCI: spinal cord injury; tSCI: traumatic spinal cord injury; mo: monthly.

[a]data listed not limited to people with SCI.

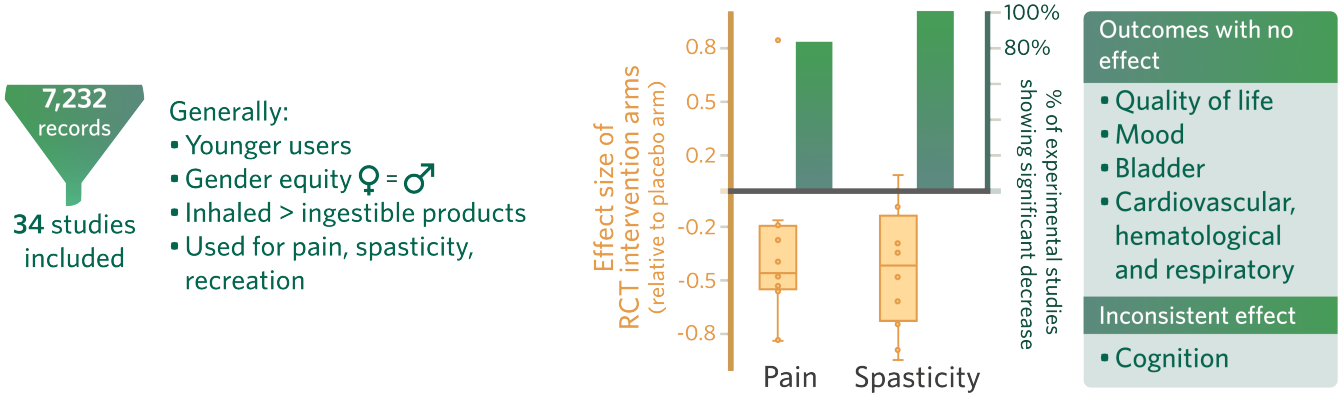

Fig. (2). Summary of the therapeutic effects of cannabinoids on patients with SCI.

Table 3. Experimental studies: effect of cannabinoids on pain.

Author, Year	Inclusion Criteria	Exclusion Criteria	Number of Participants (SCI/Total)	Male/ Female	Mean Age	Tetraplegia/ Paraplegia	Mean Time Since Injury	Intervention	Comparison	Pain Measures	Outcome	Effect Size
Randomized Control Trials (Mixed Samples)												
*Karst *et al*., 2003 [56]	Neuropathic and somatic pain for ≥6mo, stable levels of pain medications for ≥2mo. Aged 18-65y. Consent to participate in study and follow study procedures	No N-methyl-D-aspartate receptor antagonist and cannabinoid concomitant pain-relieving medications. Severe organic or psychiatric disease, pregnancy/attempting to conceive, lactation, use of any investigational drug within 30d prior to the first dose of study drug, non-German speaking	3/21	13/8	51y (21-65y)	0/3	NR	CT-3 (10.0mg–max 80.0mg) before placebo sequence f/u: 3, 8 hrs	Placebo	VRS pain, VAS pain (100-mm scale)	↓ Pain (3hrs: VAS p=0.02, VRS p=0.10) 8hrs: VAS p=0.21, VRS p=0.14)	3hr VRS: ↓0.55/↓0.50 3hr VAS: ↓0.82/↓0.52 8hr VRS: ↓0.39/↓0.54 8hr VAS: ↓0.52/↓0.17
*Wade *et al*., 2003[58]	Neurologic diagnosis and be able to identify troublesome symptoms which were stable and unresponsive to standard treatments.	History of drug or alcohol abuse, serious psychiatric illness (excluding depression associated with neurological condition), serious cardiovascular disease or active epilepsy	4/20	10/10	48y	NR	NR	CBD-rich sublingual spray (2.5mg–max 120mg/d) f/u: 2 wks	Placebo (Inert Plant Material)	VAS pain (daily 100-mm scale, 2wk 11-point scale)	↓ Pain (daily VAS p<0.05)	VAS pain/d: ↓0.45 VAS pain 2wk: ↓0.19
								THC-rich sublingual spray (2.5mg–max 120mg/d) f/u: 2 wks	Placebo (Inert Plant Material)		↓ Pain (daily VAS p<0.05)	VAS pain/d: ↓0.39 VAS pain 2wk: ↓0.82
								1:1 THC:CBD sublingual spray (2.5mg–max 120mg/d) f/u: 2 wks	Placebo (Inert Plant Material)		= Pain	VAS pain/d: ↓0.19 VAS pain 2wk: ↓0.16
*Wilsey *et al*., 2008 [59]	Adults with complex regional pain syndrome (CRPS type 1), SCI, peripheral neuropathy, or nerve injury. Previous cannabis exposure. Must refrain from smoking cannabis or taking oral synthetic delta-9-THC medications for 30d before study session	Candidates who met the criteria for severe major depressive disorder, or candidates with a history or diagnosis of schizophrenia or bipolar depression. Uncontrolled hypertension, cardiovascular disease, chronic pulmonary disease (asthma, chronic pulmonary obstructive disease), active substance abuse	6/38	20/18	46y (21-71y)	NR	6y (10mo-24y)	3.5% delta 9-THC cigarettes (9 puffs) f/u: 1, 2, 3, 4, 5, 6 hrs	Placebo	VAS pain intensity (100-mm scale), VAS pain unpleasantness, Global Impression of Change, Neuropathic pain scale, VAS allodynia, Heat pain threshold	↓ Pain (p=0.03 CI -0.0069 to -0.0003) ↓ Pain Unpleasantness (p<0.01 CI -0.33 to -0.09) ↑ Global Impression of Change of Pain (p<0.01 CI 0.064 to 0.018) ↓ Neuropathic Pain Scale (sharp, burning, aching, deep pain p<0.001; superficial p<0.04; sensitive p<0.03)	Insufficient data
								7% delta 9-THC cigarettes (9 puffs) f/u: 1, 2, 3, 4, 5, 6 hrs	Placebo		↓ Pain (p=0.04 CI -0.0068 to -0.0002) ↓ Pain Unpleasantness (p<0.01 CI -0.33 to -0.09) ↑ Global Impression of Change of Pain (p<0.01 CI 0.065 to 0.018) ↓ Neuropathic Pain Scale (sharp, burning, aching, deep pain p<0.001; superficial p<0.01; sensitive p<0.03)	Insufficient data

(Table 3) contd….

Author, Year	Inclusion Criteria	Exclusion Criteria	Number of Participants (SCI/Total)	Male/ Female	Mean Age	Tetraplegia/ Paraplegia	Mean Time Since Injury	Intervention	Comparison	Pain Measures	Outcome	Effect Size
Randomized Control Trials (Mixed Samples)												
*Rintala *et al*., 2010 [57]	Adults who had sustained an SCI ≥12 before study entry and who reported chronic (>6 mo) neuropathic pain, the intensity of which was rated as >5 at its worst on a scale of 0-10	Previous adverse reaction to any cannabinoid or sesame oil, current or history substance abuse, serious psychological or psychiatric disorder, renal or hepatic insufficiency, history of tachycardia, pregnant or nursing	7/7	5/2	50.1 ± 8.3y	¾	21.9 ± 9.3y (4-32y)	Dronabinol (5.0mg–max 20.0mg) f/u: 2, 4 wks	Placebo (diphenhydramine)	Brief Pain Inventory	= Pain	Brief Pain Inventory: ↑0.83
*Wilsey *et al*., 2016 [60]	Age 18-70y, with pain intensity >4/10, who attend the UC Davis Medical Center Spinal Cord Injury Clinic	Diagnosis of bipolar depression, schizophrenia, severe depression, or affirmation to the statements "I felt life was not worth living"; "I felt like hurting myself"; "I felt like killing myself". A history of coronary artery disease, obstructive pulmonary disease, severe liver disease, impaired renal function. Current substance use disorder.	29/42	29/13	46.4y	NR	11.6 ± 10.1y	2.9% delta 9-THC vaporized cannabis (4-8 puffs) f/u: 60, 120, 180, 240, 300, 360, 420min	Placebo	VAS 100-mm pain scale, Patient Global Impression of Change, Neuropathic Pain Scale, VAS allodynia, Heat-pain threshold	↓ Pain Intensity (60min p<0.05, 120/240min p<0.01, 300min p<0.05, 360min p<0.05, 420min p<0.05) ↑ Pain Relief (60, 120, 240, 300, 420min p<0.0001) *given second dose at 240min ↓ all neuropathic pain except itching (p<0.0001)	Insufficient data
								6.7% delta 9-THC vaporized cannabis (4-8 puffs) f/u: 60, 120, 180, 240, 300, 360, 420min	Placebo		↓ Pain Intensity (60min p<0.05, 300min p<0.05, 360min p<0.05, 420min p<0.05) ↑ Pain Relief (60, 120, 240, 300, 360min p<0.0001) *given second dose at 240min ↓ all neuropathic pain except itching (p<0.0001)	Insufficient data
Pre-/Post-Studies (SCI samples)												
Hagenbach *et al*., 2007 [55] Open-label	Terminated taking all spasmolytic medication ≥3 half-life periods before enrolling, free of illegal drugs. Spasticity without any spasmolytic treatment had to be ≥3points on the MAS in at least one muscle group	Pregnant, severe somatic and known psychiatric diseases	22/22	20/2	40.9y (19-73y)	11/11	13.3y (2-29y)	Dronabinol capsule oral (2.5mg, 5.0mg, 10.0mg) f/u: 1, 8, 43d	Baseline	6-point pain scale	↓ Pain (1d p=0.047)	

Abbreviations: ↑: increase; ↓: decrease; =: no change; *: pain studied as a primary outcome; CBD: cannabidiol; CT-3: 1',1'-dimethylheptyl-Δ8-tetrahydrocannabinol-11-oic acid in capsules; CI: confidence interval; d: day; f/u: follow-up; MAS: Modified Ashworth Scale; mo: month; NR: not reported; SCI: spinal cord injury; THC: tetrahydrocannabinol; UC: University of California; VAS: visual analog scale; VRS: verbal rating scale; wks: weeks, y: years.

Table e-6. Summary coding of studies examining the effect of cannabinoids on SCI-specific outcomes.

Outcome	n/N (%)	Effect (0/-/+/?)
Pain	5/6 (83%)	++
Spasticity	5/5 (100%)	++
Quality of life and daily function	0/3 (0%)	00
Cognition	3/6 (50%)	?
Mood and emotion	0/3 (0%)	00
Bladder function	0/3 (0%)	00
Cardiovascular, hematologic and respiratory	0/3 (0%)	00

Abbreviations: n: number of studies reporting a difference in the expected direction. N: number of identified studies of interest. (%): percentage of studies reporting differences in the expected direction. 0: no effect, 0–33% of studies reported significant differences. ?: inconsistent, 34–59% of studies reported significant differences. +/-: positive (+) or negative (−) effect, 60–100% of studies demonstrated significant differences. ≥4 studies: positive (++), negative (−−), no effect (00), inconsistent findings (??).

THC-rich sublingual spray alone caused decreased concentration ($p<0.05$), while CBD-rich and 1:1 CBD:THC had no effect on SOMC scores. Karst *et al*. [56], measured changes in processing speed, visual attention and task switching with the Trail Making Test (TMT), and found CT-3 to have no effect on time to completion. Hagenbach *et al*. [55], used the Continuous Performance Test, Divided Attention Test, and the Deux Barrages tests to measure the effect of 2.5 – 10.0 mg Dronabinol. In the placebo-controlled double-blind, parallel trial, Dronabinol increased reaction times, while the open-label phase of the study showed no change in scores after Dronabinol administration. Kogel *et al*. [76], measured the effects of 15.0 – 60.0 mg Dronabinol and found no change in concentration measured with the Weschler Memory Scale. Vaporized THC (2.9%, 6.7%) had no effect on neurocognition based on the Grooved Pegboard Test (GPT), Weschler Adult Intelligence Scale Digit Symbol Test (WAIS-III), TMT, Paced Auditory Serial Addition Test [60]. Wilsey *et al*. [59], studied cognition changes using the WAIS-III, GPT and the Hopkins Verbal Learning Test-Revised. 3.5% THC cigarettes resulted in decreased attention, learning and memory, and decreased psychomotor speed compared to placebo. The 7% THC cigarettes also decreased learning and memory [59]. The two studies by Wilsey *et al*., reported subjective effects such as "*slowed down mentally* " or "*difficulty paying attention or remembering things* " [59, 60]. Significantly more participants reported "*feeling high*", "*feeling stoned* ", "*feeling impaired* ", or having difficulty concentrating when on the active treatment compared to the placebo [56, 59, 60, 76].

Among the three SCI-specific observational studies that investigated cognition, cannabinoids were associated with negative cognitive states. These included reports of participants experiencing inertia or executive dysfunction (63%), feeling subdued or dull (50% from a sample of 537 and 19% from a sample of 51), absent-minded (29%), memory loss (27%), lethargy (26%), and drowsiness or fatigue (22% from a sample of 353 and 19% from a sample of 51) [44, 49, 75].

3.7.2. Mood and Emotion

Three experimental studies, including five therapeutic intervention arms, investigated the effects of cannabinoids on mood as a secondary outcome measure in people with SCI who did not have a history of psychological or psychiatric disorders [55, 59, 76] (Table **6**, Table **e-6**). Hagenbach *et al*. [55], found that Dronabinol (2.5 – 10.0 mg) had no significant effect on mood based on the Hamilton Rating Scale for Depression. Kogel *et al*. [76], reported a decrease in vigor and an increase in at least one dysphoric mood (anger, tension) with Dronabinol based on the Profile of Mood States questionnaire [55, 59, 76]. Wilsey *et al*. [59], found that neither 3.5% nor 7%-THC cigarettes affected VAS scores for any parameter (sad *vs*. happy; anxious *vs*. relaxed; jittery *vs*. calm; bad *vs*. good; paranoid *vs*. self-assured; fearful *vs*. unafraid). One observational study described that 13% of participants were "*feeling depressed* " after cannabinoid use [44].

3.7.3. Bladder function

Wade *et al*. [58], assessed the effects of sublingual THC-rich, CBD-rich and 1:1 CBD:THC spray on bladder function using subjective severity scales for incontinence and bladder urgency, as well as incontinence frequency per day and nocturia frequency per night, and reported no effect (Table **6**, Table **e-6**). Rectal THC increased the maximum cystometric capacity (MCC) in five of six participants, but there was no significant change in any of the other bladder function parameters (first desire to void, intra-vesical pressure, bladder compliance, postvoid residual urine volume, volume at first detrusor contraction). Administration of oral THC yielded mixed effects on MCC, with no significant change in other bladder function parameters [55]. Survey data from Dunn and Davis [63] demonstrated a 20% increase in urinary retention (from a sample of ten males) (Table **6**, Table **e-6**).

3.7.4. Cardiovascular, Hematologic and Respiratory Effects

Overall, three studies reported that cannabinoids did not impact electrocardiogram (ECG) findings, while not specifically noting if cannabinoids affected ECG parameters such as rhythm, speed or axis that might indicate tachycardia, bradycardia or an arrhythmia (Table **6**, Table **e-6**) [55, 56, 60]. Karst *et al*. [56], reported that CT-3 caused no significant changes in the measured respiratory rate (RR), heart rate (HR), or blood and hematologic chemistry (chloride, sodium, potassium, creatinine, total bilirubin, alkaline phosphatase (ALP),

Table e-7. Effect sizes and relative differences of randomized control studies of the effects of cannabinoids among adults with chronic SCI.

Outcome	Author, Year	Outcome Measure	Group	Dose	Follow-up Times	Treatment		Control			
						n	Mean*	n	Mean*	Effect size (d)** [CI]	|Hedges| (Δ)
Pain	Karst *et al*., 2003 [56]	VRS pain	CT-3 – placebo sequence AM PM	CT-3 10.0mg-80.0mg	3hrs 8hrs	10 10	-0.36 (0.47) -0.57 (0.95)	10 10	-0.11 (0.40) -0.25 (0.55)	-0.57 (0.44) [-1.44-0.34] -0.41 (0.06) [-1.28-0.49]	0.55 (↓) 0.39 (↓)
			Placebo – CT-3 sequence AM PM		3hrs 8hrs	11 11	-0.61 (1.01) -0.62 (0.74)	11 11	-0.19 (0.55) -0.29 (0.38)	-0.52 (0.81) [-1.35-0.35] -0.56 (0.59) [-1.39-0.31]	0.50 (↓) 0.54 (↓)
		VAS pain, 100-mm scale	CT-3 – placebo sequence AM PM		3hrs 8hrs	10 10	-13.07 (13.76) -15.56 (23.38)	10 10	-1.52 (12.98) -5.91 (14.82)	-0.86 (13.38) [-1.74-0.09] -0.49 (19.57) [-1.36-0.42]	0.82 (↓) 0.47 (↓)
			Placebo – CT-3 sequence AM PM		3hrs 8hrs	11 11	-13.00 (22.14) -12.39 (14.48)	11 11	-3.14 (13.11) -8.26 (29.15)	-0.54 (18.19) [-1.37-0.33] -0.18 (23.00) [-1.01-0.66]	0.52 (↓) 0.17 (↓)
	Wade *et al*., 2003 [58]	VAS pain, 100-mm scale (0=worst, 100=best possible)	CBD THC CBD:THC	2.5mg-120.0mg/d	Daily	20 20 20	54.8 (22.6) 54.6 (27.4) 51.3 (27.0)	20	44.5 (22.7)	0.46 (22.6) [-0.18-0.43] 0.40 (25.1) [-0.37-2.02] 0.27(24.9) [-0.36-0.89]	0.45 (↓) 0.39 (↓) 0.27 (↓)
		VAS pain, 11-point scale	CBD THC CBD:THC		2wks	20 20 20	3.8 (2.9) 3.5 (2.8) 3.9 (2.9)	20	4.4 (3.2)	-0.20 (3.05) [-0.81-0.43] -0.90 (1.70) [-0.37-2.02] -0.16 (3.05) [-0.78-0.46]	0.19 (↓) 0.82 (↓) 0.16 (↓)
	Wilsey *et al*., 2008 [59]	VAS pain intensity, 11-point scale	3.5% THC 7% THC	9 puffs	1, 2, 3, 4, 5, 6 hrs	36 34	NR NR	33	NR	Insufficient data	Insufficient data
	Rintala *et al*., 2010 [57]	Brief Pain Inventory, 11-point scale	Dronabinol	5.0-20.0mg/d	4wks	7	-0.27 (0.84)	5	-1.80 (2.49)	0.90 (1.70) [-0.37-2.02]	0.83
	Wilsey *et al*., 2016 [60]	VAS pain, 100-mm scale (0=worst, 100=best possible)	2.9% THC 6.7% THC	4-8 puffs	1, 2, 3, 4, 5, 6 hrs	42 42	NR NR	42	NR	Insufficient data	Insufficient data
Spasticity	Wade *et al*., 2003 [58]	NRS spasms, 100-mm scale (0=worst, 100=best possible)	CBD THC CBD:THC	2.5mg-120.0mg/d	Daily	20 20 20	54.6 (19.1) 58.4 (22.3) 55.8 (24.4)	20	47.3 (22.6)	0.35 (20.9) [-0.28-0.97] 0.49 (22.4) [-0.14-1.11] 0.36 (23.5) [-0.27-0.98]	0.34 (↓) 0.48 (↓) 0.35 (↓)
		NRS spasticity, 100-mm scale (0=worst, 100=best possible)	CBD THC CBD:THC			20 20 20	47.8 (18.5) 57.3 (22.2) 43.8 (15.6)	20	42.3 (18.1)	0.30 (18.3) [-0.33-0.92] 0.74 (20.3) [0.09-1.37] 0.09 (16.9) [0.71-0.08]	0.29 (↓) 0.75 (↓) 0.09 (↓)
		Spasticity severity, 11-point scale	CBD THC CBD:THC		2wk	20 20 20	3.8 (2.0) 3.8 (2.0) 4.1 (1.8)	20	5.4 (2.3)	-0.74 (2.15) [-1.37-(-0.09)] -0.74 (2.15) [-1.37-(-0.09)] -0.63 (2.07) [-1.25-(-0.57)]	0.73 (↓) 0.73 (↓) 0.62 (↓)

(Table e-7) contd….

Outcome	Author, Year	Outcome Measure	Group	Dose	Follow-up Times	Treatment		Control			
						n	Mean*	n	Mean*	Effect size (d)** [CI]	|Hedges| (Δ)
-		Spasticity frequency, per day	CBD THC CBD:THC			20 20 20	4.6 (2.2) 3.4 (1.8) 3.6 (1.6)	20	4.9 (2.5)	-0.36 (2.25) [-0.97-0.28] -0.97 (2.07) [-1.60-(-0.30)] -0.91 (1.98) [-1.54-(-0.24)]	0.35 (↓) 0.95 (↓) 0.89 (↓)
		AS	CBD THC CBD:THC			20 20 20	1.7 (1.2) 1.8 (1.2) 1.7 (1.1)	20	1.7 (1.0)	0.00 (1.10) [-0.62-0.62] 0.09 (1.10) [-0.53-0.71] 0.00 (1.05) [-0.62-0.62]	0.00 0.09 0.00
	Hagenbach *et al*., 2007 [55]	MAS	Oral THC	(2.5mg, 5.0mg, 10.0mg	1hr	6	7.57 (7.37)	7	12.00 (6.11)	-0.66 (6.71) [-1.73-0.50]	0.61 (↓)
	Pooyania *et al*., 2010 [77]	AS – most involved group	Nabilone	0.5-1.0mg/d	4wk	11	6.45	11	7.45	Insufficient data	Insufficient data
		AS – 8 muscle groups	Nabilone			11	26.9	11	29.45	Insufficient data	Insufficient data
		VAS spasticity, 100-mm scale (0=no spasticity, 100=most spasticity)	Nabilone			11	44.09	11	53.18	Insufficient data	Insufficient data
		Spasm frequency scale	Nabilone			11	3.45	11	3.45	Insufficient data	Insufficient data
	Wilsey *et al*., 2016 [60]	Spasticity severity scale 11-point	2.9% THC 6.7% THC	4-8 puffs	1, 2, 3, 4, 5, 6 hrs	42 42	NR NR	42	NR	Insufficient data	Insufficient data

Abbreviations: AS: Ashworth Scale, CBD: cannabidiol, MAS: modified Ashworth Scale, THC: tetrahydrocannabinol, VAS: visual analog scale, VRS: verbal rating scale, ↓: decrease. *Mean (SD), if not indicated otherwise. **Based on mean difference scores of intervention vs control group; see formula below [39]. Δ outcome change from baseline.

$$ES = \frac{(M_{TG,t2} - M_{TG,t1}) - (M_{CG,t2} - M_{CG,t1})}{SD_{pooled}} \qquad SD_{pooled} = \sqrt{\frac{(N_{TG} - 1){SD_{TG}}^2 + (N_{CG} - 1){SD_{CG}}^2}{N_{TG} + N_{CG} - 2}} \qquad \mu_{weighted} = \frac{\sum_{i=1}^{n} x_i w_i}{\sum_{i=1}^{n} w_i}$$

CG: Control Group, ES: Effect Size, M: Mean, N: number, SD: Standard Deviation, t= Time Point, TG: Treatment Group, $\mu_{weighted}$: weighted mean, w: Weights, x: Value

γ-glutamyl transferase (γ-GT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and whole blood cell count). No significant change from baseline was found in blood pressure (BP) at 3 and 8 hours after administration of CT-3 [56].

Hagenbach *et al*. [55], reported that Dronabinol and rectal-THC had no effect on HR, blood tests (hemogram, C-reactive protein, AST, ALT, γ-GT, ALP, creatinine, uric acid, sodium, potassium) or pulmonary function tests. At the 6-week follow-up, Dronabinol was associated with a reduction in BP from baseline, while BP increased with the placebo; this difference was marginally significant [55]. Wilsey *et al*. [60], implemented single-day dosing titration strategies for vaporized 2.9%- and 6.7%-THC, and reported that neither potency had an effect on RR, but caused significant increases in HR ($p<0.0001$) at 1 hour and 4 hours compared to placebo. Vaporized cannabinoids decreased both systolic and diastolic BP compared to placebo, but was not statistically significant [60]. Their study population consisted of current users (50%), ex-users (40%), and cannabinoid-naïve (10%), and found that ongoing cannabinoid use had no effect on HR, RR or BP [60]. One observational study described hypotension (15%) [49] as a notable side effect.

3.7.5. Other Side Effects

Karst *et al*. [56], reported that CT-3 led to no significant changes in weight or temperature. Other side effects reported across observational studies included dry mouth (55%), residual bad tastes (30%), amotivation (30%), dehydration (29%), risky behaviour (27%), paranoia (19%), related financial issues (19%), constipation (17%), and physical instability (11%) [44, 49, 75] (Table **6**). Less common effects also included health-related problems (6%), work-related problems (4%), nausea (4%), weight gain (4%) and hallucinations (2%) [44, 49].

4. DISCUSSION

The aims of this systematic review were to analyze cannabinoid usage patterns, reasons for use, and treatment efficacy

Table 4. Reported benefits of cannabinoid use from observational studies.

Author, Year	Study Type	Legalization (Location)	Number of Participants (SCI/Total)	Inclusion Criteria	Exclusion Criteria	Male/Female/ Transgender	Mean Age	Reported Pain Relief	Reported Spasticity Relief	Other Benefits
Dunn & Davis, 1974 [63]	Cross-sectional	Illegal (Florida, USA)	10/10	SCI patients using cannabis	-	10/0/0	NR	Relief: 50% (headache), 40% (phantom); Pain distraction (phantom): 20%	Relief: 50%	Pleasant sensations: 50%
Malec *et al*., 1982 [64]	Cross-sectional	Illegal (Wisconsin, USA)	43/43	SCI patients	-	38/5/0	NR	NR	Relief: 88% (Complete relief 38%, reduction to mild 46%, severe to moderate 4%)	NR
Warms *et al*., 2002 [68]	Cross-sectional	MC legal starting Nov 1998, study V1 Feb 1997 – Jul 1998, V2 Aug 1998 – June 2000 (Washington, USA)	471/471	18+ age, 6+ mo since SCI	-	334/137/0	42.5 ± 13.2 (18-84)	Pain helpfulness: 4.25 ± 0.76 (max 5); Most effective pain treatment	NR	Pain relief greater than opioids, mexiletine, baclofen, acetaminophen, TCAs, NSAIDs, gabapentin, carbamazepine, *etc*
Grotenhermen & Schnelle[a], 2003 [51]	Cross-sectional	Dronabinol prescription and Δ9-THC special permit (Germany) and permit (Switzerland)	4/165	Members of Association for Cannabis as Medicine	No severe disease	101/64/0	Median age: 40.3 ± 12.4 (16-87)	NR	NR	Large disease improvement: 75%, small improvement: 13%, no improvement: 2%, unknown: 7%, no answer: 3%; Large improvement over other drugs: 69%, small improvement: 7%, no improvement: 3%, unknown: 18%, no answer: 4%
Gorter[a], 2005 [52]	Cross-sectional	MC legal (Netherlands)	?/107	Members of Multiple Sclerosis society	-	48/59/0	Median age: 58.0	NR	NR	Efficacy: excellent 18%, good 47%, somewhat 18%, none 18%; Statistical significance in greater efficacy with inhalation vs. oral
Cardenas & Jensen, 2006 [53]	Cross-sectional	MC legal (Washington, USA)	117/117	18+ age, tSCI, chronic pain	Incomplete questionnaires	85/32/0	48.8 ± 11.7 (21-79)	Relief: 6.62 ± 2.54 (max 10) Benefit duration: 9%: min, 80%: hr, 3%: days, 3%: mo, 6%: y. Most effective pain treatment	NR	Pain relief greater than opioids, mexiletine, baclofen, acetaminophen, TCAs, NSAIDs, gabapentin, carbamazepine, *etc*
Mahoney *et al*., 2007 [69]	Interview	Illegal (Texas, USA)	24/24	1+ y since SCI, spasticity, English language	-	17/7/0	45.1 (21-68)	NR	Prevents, modulates and stops spasms	NR

(Table 4) contd….

Author, Year	Study Type	Legalization (Location)	Number of Participants (SCI/Total)	Inclusion Criteria	Exclusion Criteria	Male/ Female/ Transgender	Mean Age	Reported Pain Relief	Reported Spasticity Relief	Other Benefits
Aggarwal *et al.*[a], 2009 [46]	Retro-spective chart review	MC legal (Washington, USA)	5/139	18+ age, pain clinic patients, access to MC with valid doctor documen-tation	Cannabinoid receptor 1 blocker drug rimonabant	88/51/0	Median age: 48 (18-84)	Chronic pain relief; often described as the most effective pain treatment	NR	Preferred for less side effects; adjunctive use with opioids reduced opioid dosages and 6% used to reduce opioid dependence
Heutink *et al*., 2011 [70]	Cross-sectional	MC legal starting 2003, study 1990-2005 (the Netherlands)	279/279	18+ age, SCI rehab patients, living in com-munity	-	173/106/0	51.3 ± 14.0 (25-81)	(Alcohol and cannabis pooled) Largely effective 83%, somewhat effective 17%, not effective 0%	NR	NR
Shroff, 2015 [54]	Interview	MC legal (Canada)	53/53	19-65 age, 1+ years since SCI, BC resident, member of paraplegic association	-	42/11/0	NR	NR	NR	Preferred for less side effects
Andresen *et al*., 2017 [44]	Cross-sectional	MC legal starting 2011, study 1990-2012 (Den-mark)	537/537	Inclusion: 18+ age, acquired tSCI, rehab clinic patients	Incomplete question-naires	413/124/0	54.6 ± 14.6 (18-88)	Relief: good 35%, very good 24%	Relief: good 32%, very good 27%	NR
Bruce *et al*[a]., 2018 [50]	Interview	MC legal (Illinois, USA)	6/30	18+ age, smoked MC in past 3 mo, qualifying health condition for MC	-	19/11/0	44.6 ± 15.9	NR	NR	Preferred over other pain treatments for quick action, long effects, symptom relief, less side effects; adjunctive use with opioids reduced opioid dose and dependence
Bourke *et al*., 2019 [72]	Interview	Illegal (New Zealand)	8/8	18+ age, SCI patients using cannabis for pain, residing in New Zealand, English speaking,	Comorbid conditions inhibiting communica-tion and participation in the interview	6/2/0	Age 20-39: n = 1, 40-59: n= 5, 60+: n=2	Pain relief improving function, community participation and de-creased disability	NR	Preferred for relatively lower fatigue and drowsiness as of prescribed medications Sleep improvement Quality of life improvement
Stillman *et al*., 2019 [75]	Cross-sectional	39 states in USA, not disclosed; mixed legality	353/353	SCI patients included in mailing lists maintained by Thomas Jeffer-son University, University of Washington at Seattle, and University of Alabama at Birmingham	-	183/107/3	52.74 (19-82)	NR	NR	Muscle relaxation: 90% Sleep promotion: 84% Well-being: 75% Anxiety relief: 70% Appetite promotion: 53% All prevalence of positive effects from cannabis were rated higher than prescription medications Cannabis use: lower preva-lence of dehydration, memory loss, lethargy, drowsiness, constipation

Abbreviations: BC: British Columbia; d: days; hr: hours; MC: medical cannabis; min: minutes; mo: months; NR: not reported; NSAIDs: nonsteroidal anti-inflammatory drugs; SCI: spinal cord injury; TCAs: tricyclic antidepressants; Δ9-THC: delta-9-tetracannabidiol; tSCI: traumatic spinal cord injury; y: years. [a]data listed not limited to people with SCI.

Table 5. Experimental studies: effect of cannabinoids on spasticity.

Author, Year	Inclusion Criteria	Exclusion Criteria	Number of Participants (SCI/Total)	Male/ Female	Mean Age	Tetraplegia/ Paraplegia	Mean Time Since Injury	Inter-vention	Compari-son	Spasticity Measures	Outcome	Effect Size
Randomized Control Trials (Mixed Samples)												
*Wade *et al*., 2003 [58]	Neurologic diagnosis and be able to identify troublesome symptoms which were stable and unresponsive to standard treat-ments.	History of drug or alcohol abuse, serious psychiatric illness (excluding depres-sion associated with neurological condition), serious cardiovascular disease or active epilepsy	4/20	10/10	48y	NR	NR	CBD-rich sublingual spray (2.5mg–max 120mg/d) f/u: 2 wks	Placebo (Inert Plant Material)	NRS spasticity, AS, 10-point spasticity severity scale; spasm frequen-cy/day	↓ Spasticity (2wk NRS p<0.05)	NRS spasm/d: ↓ 0.34 NRS spastici-ty/d: ↓ 0.29 Severity 2wk: ↓ 0.73 Frequency 2wk: ↓ 0.35
								THC-rich sublingual spray (2.5mg–max 120mg/d) f/u: 2 wks	Placebo (Inert Plant Material)		↓ Spasticity (daily, 2wk NRS p<0.05)	NRS spasm/d: ↓ 0.48 NRS spastici-ty/d: ↓ 0.75 Severity 2wk: ↓ 0.73 Frequency 2wk: ↓ 0.95
								1:1 THC:CBD sublingual spray (2.5mg–max 120mg/d) f/u: 2 wks	Placebo (Inert Plant Material)		↓ Spasticity (daily, 2wk NRA p<0.05)	NRS spasm/d: ↓ 0.35 NRS spastici-ty/d: ↓ 0.09 Severity 2wk: ↓ 0.62 Frequency 2wk: ↓ 0.89
*Hagenbach *et al*., 2007 [55] **RCT phase	Terminated taking all spasmolytic medication ≥3 half-life periods before enrolling, free of illegal drugs. Spasticity without any spasmolytic treatment had to be ≥3points on the MAS in at least one muscle group	Pregnant, severe somatic and known psychiatric diseases	13/13	11/2	40.9y (29-66y)	5/8	14.3y (3y-29y)	Dronabinol capsule oral (2.5mg, 5.0mg, 10.0mg) f/u: 1, 8, 43d	Placebo (sesame oil)	MAS, 7-point spasticity severity scale	↓ Spasticity (p=0.001 placebo of this phase vs open label of oral phase) (day one self-rating p=0.033)	MAS: ↓ 0.61
**Non-RCT phase			22/22	20/2	40.9y (19-73y)	11/11	13.3y (2-29y)	Dronabinol capsule oral (2.5mg, 5.0mg, 10.0mg) f/u: 1, 8, 43d	Baseline		↓ Spasticity (AS at 1/8d p<0.001, 43d p<0.05)	-
			8/8	8/0	48.8y (32-66y)	5/3	15.5y (5-28y)	Rectal THC (5.0mg, 10.0mg) f/u: 1, 8, 43d	Baseline		↓ Spasticity (AS at 1/8/43d p<0.05)	-
*Pooyania *et al*., 2010 [77]	Aged 18-65 with a level of injury at C5 or below, and injury occurred more than 1 year previously. Stable neurologic level, with moderate spasticity (>3 AS). Spasticity medica-tions had to be unchanged for at least 30 days before inclusion and no botulinum toxin injections >4 months	History of heart disease, psychotic disorders, schizophrenia, or any active psychologic disor-der. Previously document-ed sensitivity to marijuana or other cannabinoid agents, severe liver dysfunction, cognitive impairment, a major illness in another body area, fixed tendon contractures. Pregnant or nursing. History of drug dependen-cy, smoked cannabis <30d before study onset, or unwilling to not smoke during the study	12/12	12/0	42.4y	6/6	NR	Nabilone (0.5mg-1.0mg/d) f/u: 4wks	Placebo	AS, Spasm frequency scale, VAS spasticity, Pendulum test, Global Impression of Change (subject/ clinician)	↓ Spasticity ([a]AS in most spasticity group p=0.003, AS in 8 muscle groups p=0.001)	Insufficient data

(Table 5) contd….

Author, Year	Inclusion Criteria	Exclusion Criteria	Number of Participants (SCI/Total)	Male/ Female	Mean Age	Tetraplegia/ Paraplegia	Mean Time Since Injury	Intervention	Comparison	Spasticity Measures	Outcome	Effect Size
Randomized Control Trials (Mixed Samples)												
*Wilsey *et al*., 2016 [60]	Age 18-70, with pain intensity >4/10, who attend the UC Davis Medical Center Spinal Cord Injury Clinic	Diagnosis of bipolar depression, schizophrenia, severe depression, or affirmation to the statements "I felt life was not worth living"; "I felt like hurting myself"; "I felt like killing myself". A history of coronary artery disease, obstructive pulmonary disease, severe liver disease, impaired renal function. Current substance use disorder.	29/42	29/13	46.4y	NR	11.6 ± 10.1y	2.9% delta 9-THC vaporized cannabis (4-8 puffs) f/u: 60, 120, 180, 240, 300, 360, 420min	Placebo	11-point spasticity severity scale (spasms, pain, muscle stiffness), Global Impression of Change	↓ Spasticity (420min p<0.0001) ↑ Relief (p=0.0227)	Insufficient data
								6.7% delta 9-THC vaporized cannabis (4-8 puffs) f/u: 60, 120, 180, 240, 300, 360, 420min	Placebo		= Spasticity	Insufficient data
Pre-/Post-Studies (SCI samples)												
*Kogel *et al*., 1995 [76]	SCI staff selected. Chronic problematic spasticity that has not responded to more commonly prescribed spasmolytic medications.	-	5/5	5/0	41y (28-55y)	5/0	6mo-9y	Dronabinol (15.0 mg – 60.0mg/d) f/u: 5d	Baseline	Pendulum Drop Test	↓ Spasticity	

Note: [a]:clinically meaningful change in AS as defined as a decrease of 1 point. ↑: increase; ↓: decrease; =: no change; *: pain studied as a primary outcome; AS: Ashworth Scale; CBD: cannabidiol; d: day; f/u: follow-up; MAS: Modified Ashworth Scale; mo: month; NR: not reported; NRS: numerical rating scale; SCI: spinal cord injury; THC: tetrahydrocannabinol; UC: University California; wks: weeks, y: years.

and safety, in people with SCI. The reviewed evidence shows cannabinoid users tended to be single, male, and younger compared to non-users, and the preferred route of administration was smoking. The observational studies reported that cannabinoids were preferred over traditional analgesics due to an earlier onset and longer duration of action, greater therapeutic efficacy, and a relatively limited side effect profile. Interestingly, many studies involved adjunct use of cannabinoids with concurrent substances, including opioids. Preliminary results from both observational and experimental studies suggest that cannabinoids may effectively manage pain and spasticity in people with SCI. The most significant side effects were "*fatigue*", "*feeling high*" or "*feeling stoned* ", and "*difficulty concentrating*". However, experimental studies did not show changes in objectively measured parameters; such as BP, RR, temperature, and blood biomarkers. Acute responses to cannabinoids, including euphoria, feelings of detachment and relaxation could be hypothesized as the basis for subjective decreases in pain [80]. This was addressed by Wilsey *et al*. [60], who controlled for psychoactive side-effects and determined that the main effect of THC remained significant. Instead, THC-mediated analgesia may be related to reduced subjective unpleasantness associated with amygdala activity [81] in acute pain, and decreased functional connectivity between sensorimotor and affective cortical regions in acute pain [81] and chronic NPP [82].

The effect of cannabinoids on BP is important to reveal because people with SCI at or above the sixth thoracic level commonly experience orthostatic hypotension (OH) and low resting BP [83]. The studies that investigated the effect of cannabinoids on BP in people with SCI included samples slightly biased towards lower levels of injury (tetraplegia, n=11, paraplegia, n=14), which may suggest more stable baseline BP, and may explain the relatively low incidence of hypotensive events.

SCI is also associated with metabolic dysfunctions, and as much as 50% of the SCI population have abnormal fatty infiltrates of the liver [84]. Preliminary studies have suggested that cannabinoids and synthetic analogues were possibly hepatotoxic; however, cannabinoid use has been associated with lower levels of non-alcoholic liver disease [85, 86]. Despite no significant changes in liver enzymes across these studies, the mechanisms of cannabinoids' effect on the liver are not well understood and warrant further investigation, particularly in the SCI population.

Concrete conclusions regarding the efficacy of cannabinoids could not be made due to the poor quality of the studies. The observational studies included in this systematic review shared common pitfalls. Samples were often small or lacked justification for their sample size, and sometimes were not SCI-specific. Moreover, these studies were cross-sectional, did not measure different levels of cannabis exposure, did not account for potential confounders and often lacked basic study information, including injury demographics. For the experimental studies, major methodological issues include small and heterogeneous samples, varying cannabinoid

Table 6. Observational studies: reported side effects from cannabinoids.

Author, Year	Inclusion Criteria	Exclusion Criteria	Number of Participants (SCI/Total)	Male/ Female/ Transgender	Mean Age	Tetraplegia/ Paraplegia	Mean Time Since Injury	Side Effects
Observational Studies								
Dunn & Davis, 1974 [63]	SCI patients using cannabis	-	10/10	10/0	NR	NR	NR	Urinary retention: 20%
Heinemann *et al*., 1991 [65]	13-66 age, 2+ years since tSCI, English language, no cognitive impairment	-	43/43	38/5	NR	NR	NR	Marijuana use problems 6 months pre-SCI: 21%, post-SCI: 13% Needing help with marijuana use problems pre-and post-SCI: 1%
Grotenhermen & Schnelle[a], 2003 [51]	Members of Association for Cannabis as Medicine	No severe disease	4/165	101/64	Median age: 40.3 ± 12.4 (16-87)	NR	NR	Side effects; none 73%, moderate 22%, no answer 4% Withdrawal; none 68%, moderate 18%, strong 3%, unknown 12%
Gorter[a], 2005 [52]	Members of Multiple Sclerosis society	-	?/107	48/59	Median age: 40.3 ± 12.4 (16-87)	NR	NR	Dry mouth: 27%, sleepiness: 14%, euphoria: 13%, loss of concentration: 12%, feeling high: 11%; More frequent side effects in first few months of intake
Aggarwal *et al*[a]., 2009 [46]	18+ age, pain clinic patients, access to MC with valid doctor documentation	Cannabinoid receptor 1 blocker drug rimonabant	5/139	88/51	Median age: 48 (18-84)	NR	NR	No side effects with MC
Shroff, 2015 [54]	19-65 age, 1+ years since SCI, BC resident, member of paraplegic association	-	53/53	42/11	NR	NR	NR	Incapacitation
Andresen *et al*., 2017 [44]	Inclusion: 18+ age, acquired tSCI, rehab clinic patients	Incomplete questionnaires	537/537	413/124	54.6 ± 14.6 (18-88)	247/263, unknown: 27	18.2 ± 12.8	Inertia: 63%, feeling subdued: 50%, absent-minded: 29%, risky behaviour: 27%
Clark *et al*., 2017 [47]	18+ age, 1+ year since tSCI, some residual impairment	No painful condition, no prescription pain med	1619/1619	1166/453	49.3 ± 14.2	453/1166	11.5 ± 9.2	Frequent MC use 1.8x pain med misuse, occasional MC use 2.7x pain med misuse
Hawley *et al*., 2018 [49]	Cross-sectional	MC and recreational legal (Colorado, USA)	51/116	95/21/0	47.1 ± 13.8 (22-74)	Tetra ABC: 38, para ABC: 31, tetra/para D: 41, unknown: 5	13.0	Amotivation: 30%, social stigma: 26%, other: 22%, feeling dull: 19%, fatigue: 19%, paranoia: 19%, low blood pressure: 15%, physical instability: 11%
Bourke *et al*., 2019 [72]	18+ age, SCI patients using cannabis for pain, residing in New Zealand, English speaking	Comorbid conditions inhibiting communication and participation in an interview	8/8	6/2/0	Age 20-39: n = 1, 40-59: n= 5, 60+: n=2	Tetra: 6 Para: 2	NR	Dysphoria: detrimental effect on the mind and ability to participate within the community
Stillman *et al*., 2019 [75]	Cross-sectional	39 states in USA, not disclosed; mixed legality	353/353	183/107/3	52.74 (19-82)	NR	17.49	Dry mouth: 55%, residual bad taste: 30%, dehydration: 29%, memory loss: 27%, lethargy: 26%, drowsiness: 22%, constipation: 17%

Abbreviations: BC: British Columbia; MC: medical cannabis; min: minutes; NR: not reported; SCI: spinal cord injury; tSCI: traumatic spinal cord injury. [a]data listed not limited to people with SCI.

Table 7. Experimental studies: reported side effects from cannabinoids.

Author, Year	Inclusion Criteria	Exclusion Criteria	Intervention	Comparison	Side Effects
Randomized Control Trials (Mixed Samples)					
Karst *et al*., 2003 [56]	Neuropathic and somatic pain for ≥6mo, stable levels of pain medications for ≥2mo. Aged 18-65y. Consent to participate in study and follow study procedures	No N-methyl-D-aspartate receptor antagonist and cannabinoid concomitant pain-relieving medications. Severe organic or psychiatric disease, pregnancy/attempting to conceive, lactation, use of any investigational drug within 30d prior to first dose of study drug, non-German speaking	CT-3 (10.0mg–max 80.0mg) f/u: 3, 8 hrs	Placebo	↑ Fatigue[f]; ↑ Dry mouth[f] ; ↑ Limited power of concentration[f]; ↑ Pain[f]; = Objective concentration; = Vitals (RR, HR, BP, wt, temp, ECG, hematologic and blood chemistry)
Wade *et al*., 2003 [58]	Neurologic diagnosis and be able to identify troublesome symptoms which were stable and unresponsive to standard treatments	History of drug or alcohol abuse, serious psychiatric illness (excluding depression associated with neurological condition), serious cardiovascular disease or active epilepsy	CBD-rich sublingual spray (2.5mg–max 120mg/d) f/u: 2 wks	Placebo (Inert Plant Material)	= Objective concentration; = Bladder function; = Daily functioning
			THC-rich sublingual spray (2.5mg–max 120mg/d) f/u: 2 wks	Placebo (Inert Plant Material)	↓ Objective Concentration (SOMC)[j]; ↑ Appetite (daily VAS)[j]; = Bladder function; = Daily functioning
			1:1 THC:CBD sublingual spray (2.5mg–max 120mg/d) f/u: 2 wks	Placebo (Inert Plant Material)	= Objective concentration; = Bladder function; = Daily functioning; ↑ Sleep (daily VAS)[j]
Hagenbach *et al*., 2007 [55] *RCT phase	Terminated taking all spasmolytic medication ≥3 half-life periods before enrolling, free of illegal drugs. Spasticity without any spasmolytic treatment had to be ≥3points on the MAS in at least one muscle group	Pregnant, severe somatic and known psychiatric diseases	Dronabinol capsule oral (2.5mg, 5.0mg, 10.0mg) f/u: 1, 8, 43d	Placebo (sesame oil)	↑ Reaction Time; = Vitals (HR, BP, ECG, hematologic and blood chemistry); = Mood; = Functional independence
*Non-RCT phase			Dronabinol capsule oral (2.5mg, 5.0mg, 10.0mg) f/u: 1, 8, 43d	Baseline	↓ Systolic BP; ↑ Vital capacity (43d)[g]; = Mood; = Functional independence; = objective concentration; = Bladder function; ↑ Fatigue (36%); ↑ Dry mouth (32%); ↑ Anxiety (32%); ↑ Disturbance of attention (27%); ↑ Pain (23%); ↑ Dizziness (23%)
			Rectal THC (5.0mg, 10.0mg) f/u: 1, 8, 43d	Baseline	↑MCC (43d)[k]; = Vitals (HR, BP, ECG, hematologic and blood chemistry); = Mood; = Functional independence
Wilsey *et al*., 2008 [59]	Adults with complex regional pain syndrome (CRPS type 1), SCI, peripheral neuropathy, or nerve injury. Previous cannabis exposure. Must refrain from smoking cannabis or taking oral synthetic delta-9-THC medications for 30d before study session	Candidates who met the criteria for severe major depressive disorder, or candidates with a history or diagnosis of schizophrenia or bipolar depression. Uncontrolled hypertension, cardiovascular disease, chronic pulmonary disease (asthma, chronic pulmonary obstructive disease), active substance abuse	3.5% delta 9-THC cigarettes (9 puffs) f/u: 1, 2, 3, 4, 5, 6 hrs	Placebo	↑ "Feeling high"[j]; ↑ "Feeling stoned"[j]; ↑ "Impaired"[d]; ↑ Sedation[d]; ↑ Hunger[b]; ↓ Attention; ↓ Learning/memory; ↓ Psychomotor speed; ↑ "Good drug effect"[b]; ↑ Calmness[i]
			7% delta 9-THC cigarettes (9 puffs) f/u: 1, 2, 3, 4, 5, 6 hrs	Placebo	↑ "Feeling high"[b]; ↑ "Feeling stoned"[c]; ↑ "Bad drug effect"[d]; ↑ "Impaired"[d]; ↑ Sedation[e]; ↑ Hunger[e]; ↓ Learning/memory; ↑ "Good drug effect"[e]; ↑ HR (immediately); = Mood; = Spasticity ; = Neurocognition (overall)
Pooyania *et al*., 2010 [77]	Aged 18-65 with a level of injury at C5 or below, and injury occurred more than 1 year previously. Stable neurologic level, with moderate spasticity (>3 AS). Spasticity medications had to be unchanged for at least 30 days before inclusion and no botulinum toxin injections >4mo	History of heart disease, psychotic disorders, schizophrenia, or any active psychologic disorder. Previous documented sensitivity to marijuana or other cannabinoid agents, severe liver dysfunction, cognitive impairment, a major illness in another body area, fixed tendon contractures. Pregnant or nursing. History of drug dependency, smoked cannabis <30d before study onset, or unwilling to not smoke during the study	Nabilone (0.5mg-1.0mg/d) f/u: 4wks	Placebo	↑ Drowsiness (27.2%); ↑ Dry mouth (18.1%); ↑ Asthenia (18.1%); ↑ Vertigo (18.1%)

(Table 7) contd….

Author, Year	Inclusion Criteria	Exclusion Criteria	Intervention	Comparison	Side Effects
Randomized Control Trials (Mixed Samples)					
Rintala *et al*., 2010 [57]	Adults who had sustained an SCI ≥12 before study entry and who reported chronic (>6mo) neuropathic pain, the intensity of which was rated as >5 at its worst on a scale of 0-10	Previous adverse reaction to any cannabinoid or sesame oil, current or history substance abuse, serious psychological or psychiatric disorder, renal or hepatic insufficiency, history of tachycardia, pregnant or nursing	Dronabinol (5.0mg–max 20.0mg) f/u: 2, 4 wks	Placebo (diphenhydramine)	↑ Constipation; ↑ Fatigue; ↑ Dry mouth; ↑ Abdominal discomfort
Wilsey *et al*., 2016 [60]	Age 18-70, with pain intensity >4/10, who attend the UC Davis Medical Center Spinal Cord Injury Clinic	Diagnosis of bipolar depression, schizophrenia, severe depression, or affirmation to the statements "I felt life was not worth living"; "I felt like hurting myself"; "I felt like killing myself". A history of coronary artery disease, obstructive pulmonary disease, severe liver disease, impaired renal function. Current substance use disorder.	2.9% delta 9-THC vaporized cannabis (4-8 puffs) f/u: 60, 120, 180, 240, 300, 360, 420min	Placebo	↑ "Good Drug Effect"[a]; ↑ "Bad Drug Effect"[a]; ↑ High[a]; ↑ Drunk[a]; ↑ Stoned[a]; ↑ Sedated[a]; ↑ Nausea[a]; ↑ Changes Perceiving Time/Space[a]; ↑ HR (immediately); ↑ calmness; = Neurocognition (overall)
			6.7% delta 9-THC vaporized cannabis (4-8 puffs) f/u: 60, 120, 180, 240, 300, 360, 420min	Placebo	↑ Confused[a]; ↑ Desires More[a]; ↑ Hungry[a]; ↑ Difficulty Paying Attention/ Remembering Things[a]; ↑ "Good Drug* Effect"[a]; ↑ "Bad Drug Effect"[a]; ↑ High*[a]; ↑ Drunk*[a]; ↑ Impaired*[a]; ↑ Stoned*[a]; ↑ Sedated*[a]; ↑ Nausea[a]; ↑ Changes Perceiving Space*/Time[a]
Pre-/Post-Studies (SCI samples)					
Kogel *et al*., 1995 [76]	SCI staff selected. Chronic problematic spasticity that has not responded to more commonly prescribed spasmolytic medications.	NR	Dronabinol (15.0 mg - 60.0mg/d) f/u: 5d	Baseline	↓ Subjective Concentration; ↓ vigor; = objective concentration; ↑ ≥1 dysphoric mood scale

Abbreviations: ↑: increase; ↓: decrease; =: no change; [a]data listed not limited to people with SCI; AS: Ashworth Scale; BP: blood pressure; CBD: cannabidiol; CT-3: 1',1'-dimethylheptyl-Δ8-tetrahydrocannabinol-11-oic acid in capsules; d: day; ECG: electrocardiogram; f/u: follow-up; HR: heart rate; MAS: Modified Ashworth Scale; MC: Medical Cannabis; MCC: maximal cystometric capacity; mo: month; N/A: not applicable; NR: not reported; RR: respiratory rate; SOMC: short orientation-memory-cognition test; temp: temperature; THC: tetrahydrocannabinol; UC: University California; VAS: visual analog scale; wt: weight; y: year. *denotes that higher dose was significant vs lower dose; [a]denotes p<0.0001; [b]denotes p<0.001; [c]denotes p=0.001; [d]denotes p=0.003; [e]denotes p<0.01; [f]denotes p=0.02; [g]denotes p=0.028; [h]denotes p=0.03; [i]denotes p<0.03; [j]denotes p<0.05; [k]denotes p=0.075.

formulations and doses, varying concurrent medication use among participants, diverse and missing outcome measures, inconsistent comparison treatments, and missing chronic follow-up. For these reasons, a meta-analysis of these quantitative data and additional Grading of Recommendations, Assessment, Development and Evaluations was deemed ill-suited. Given the low level of evidence from existing literature, the NIH assessment tool was apt to provide an indication of the quality of studies and biases for a range of study designs. Moreover, despite similar study outcomes, the tools used to measure these outcomes and timepoints of measurement were inconsistent between studies, making it difficult to compare mean differences. Cannabinoids showed a statistically significant reduction of 83% in pain and 100% in spasticity among the experimental studies. However, clinically meaningful changes in VAS pain scores were not reported by any studies, whereas, the one study that measured spasticity through MAS showed a clinically meaningful decrease [55]. Further, few studies reported effect sizes or sufficient data to calculate effect sizes, thus precluding a comprehensive meta-analysis (Table **e-7**). Of the effect sizes calculated from RCTs, the overall effects of cannabinoids on decreasing pain and spasticity were inconsistent [39]. While the magnitude of the effect sizes varied considerably, all experimental studies showed cannabinoids significantly decreased pain, except for one poor-quality study, where they were unable to show any statistically significant change in pain. This paradoxical relationship between statistical and clinical significance, as well as effect size magnitudes, further confounds physicians' recommendations for the use of cannabinoids in persons with SCI.

Other work on this topic has come to similar, inconclusive interpretations of the therapeutic effects of cannabinoids in the SCI population. Empirical data is currently not robust enough, coupled with the difficulty of conducting rigorous randomized research in individuals with symptom complexes that are challenging to measure precisely [87]. A systematic review by Hagen *et al*. [88], which focused on both NPP and spasticity-related pain after SCI, included three studies which investigated the effects of cannabinoids. Hagen *et al*. [88], determined those studies to be too limited to allow certain conclusions regarding the efficacy of cannabinoids. Similarly, The National Academy of Sciences concluded there was insufficient evidence to support or refute the efficacy of cannabinoids as a treatment for spasticity in patients with paralysis due to SCI [87]. While sufficient conclusions cannot be made due to the low-quality evidence and small sample sizes that prevented a comprehensive meta-analysis, this systematic review presents an up-to-date search of the evidence, with a meaningful quantitative analysis given the limited data and a summary of the ongoing clinical trials. Furthermore, this systematic review, after synthesis of the available evidence, highlights the requirement for rigorous RCTs in the future.

The sample sizes of the experimental studies ranged from 5 to 42 participants, and among those, the number of SCI participants ranged from 3 to 29. These studies with heterogenous populations did not specify symptomatic relief in the SCI participants, therefore, there was a lack of SCI-specific conclusions. Furthermore, demographic data was often unreported, including the level of injury, time since injury, the ratio of males to females, and age. As a result, we were unable to distinguish the efficacy of cannabinoids for specific injury characteristics or participant demographics.

None of the observational studies examined the relationship between dosages and efficacy; only two of 22 studies reported mean dose. Among the experimental studies, there was high variability in the formulations and doses of cannabinoid interventions tested. This dose variability was present between and within studies. Most studies used self-titrated, variable dosing strategies due to the variability in individual responses to cannabinoids, balancing symptomatic efficacy and safety. For those studies that compared interventions of different potencies of THC [59, 60], there was no significant difference in analgesic effects between the two THC potencies (3.5% *vs*. 7%; 2.9% *vs*. 6.7%), but there were significant differences in the prevalence of side effects, suggesting that individuals may use lower therapeutic THC doses, while avoiding common side effects. In experimental studies that use purified forms of synthetic THC alone, it is possible that the results may not corroborate the subjective reports of observational studies. Recreational cannabis formulations, which are often smoked, contain hundreds of cannabinoids and in different ratios. It has been proposed that THC and CBD have synergistic effects that modulate treatment efficacy [89]. Therefore, further research is required to delineate specific cannabinoids and ratios of these to optimize therapeutic effects.

A significant number of trials involved the adjunct use of cannabinoids with other substances (n=6), allowing participants to continue their current anti-spastic or analgesic pharmacologic regimens. It is therefore, unclear, whether the therapeutic effects or side effects are due to cannabinoids themselves, or potential interactions with other medications. A study conducted on physically healthy individuals showed that concurrent use of cannabinoids with opioids can decrease the necessary opioid dose for comparable analgesic effects, without the increased potential of cannabinoid abuse [90]. Therefore, this suggests that the combination of cannabinoids and opioids may result in the safest and most effective analgesic effect. Moreover, cannabinoid use as an alternative or adjunctive treatment may have the potential as a harm reduction method due to the considerable side effects, toxicity, and addiction potential associated with opioids and other pain medications [46, 50]. However, clinicians may be reluctant to combine these medications until more information on their interactions is provided in humans with SCI. In future cannabinoid studies where concomitant medications are allowed, concomitant medications should be recorded for additional analysis. In the United States, there appears to be a correlation between states that have legalized cannabis and a decline in opioid-related overdose deaths, although the data is difficult to interpret without a thorough understanding of the interactions of these drugs [91].

A possible limitation of the systematic review itself was the narrow search terms for cannabinoids. While many synonyms for cannabis were included in the search, given the vast synthetic forms of cannabinoid receptor ligands, possible papers with interventions with molecular-based names may have been missed. Furthermore, part of the inclusion criteria required included studies to be peer-reviewed, excluding grey literature that could have been valuable since the medicinal properties of cannabis are still highly debated. This inclusion criteria also eliminated clinical trial results that had not yet been published in peer-reviewed journals. However, a review of the clinical trials on clinicaltrials.gov, International Standard Randomised Controlled Trial Number, and Australian New Zealand Clinical Trials Registries involving participants with SCI and cannabinoid interventions have been summarized (Table **e-8**). Furthermore, our systematic review protocol was not registered, which may have introduced unintentional bias [92].

4.1. Future Directions and Considerations

Overall, the search yielded very few RCTs that evaluated the efficacy of cannabinoids for pain and spasticity in people with SCI. Several inconsistencies may be attributed to variability in doses and formulations, routes of administration and the outcome measures tested. Nevertheless, the results are promising and implicate the need for chronic use, longitudinal studies in the future. While this systematic review provides preliminary evidence that the short-term use of cannabinoids has beneficial effects in people with SCI, further research is warranted. Additional trials that adhere to Consolidated Standards of Reporting Trials should be followed, use double-blinding, have standardized outcome measures and dosage conditions, and have more homogenous SCI-specific populations with larger sample sizes are warranted. At this time, there is not enough good quality evidence to help clinicians decide when or how to use cannabinoids for their patients with SCI.

The studies included in this systematic review often did not report bladder, bowel, and sexual functioning or BP as outcome measures, an important limitation and an area of development for future studies. These are common secondary complications following SCI [93] as a result of either partial or total loss of supraspinal control [94]. Bladder irritation, bowel distention, sexual arousal/ejaculation and pain after SCI can trigger life-threatening episodes of hypertension ($\geq$ 20 mmHg) known as autonomic dysreflexia (AD) [95] in people with SCI at or above the sixth thoracic level [96]. Cannabinoid use can lead to reduced visceral sensation and abdominal pain [97], but it is unclear if it can inhibit visceral stimuli that trigger AD during bowel management in people with SCI. If cannabinoid use has the potential to modulate afferent inputs, it could reduce the incidence and/or severity of AD experienced due to bladder/bowel distension and/or sexual intercourse. Cannabinoid receptors have been identified in the gut [97] and bladder, likely affecting micturition [98], but there is a paucity of data for their effects with SCI. The benefits of cannabinoids have been shown in other neurological conditions like MS, with reduced urinary incontinence [99], urgency, frequency and nocturia [100]. Increased complete spontaneous bowel movement and relief in constipation

Table e-8. Clinical trials conducted on adults with SCI with cannabinoids interventions searched February 29th, 2020.

Clinical Trial Name	Registry, Identifier (Status)	Phase	Conditions	Interventions	Inclusion Criteria	Exclusion Criteria	Primary Outcomes Measured	Secondary Outcomes Measured
Cannabinoids and an Anti-inflammatory Diet for the Treatment of Neuropathic Pain after Spinal Cord Injury	Clinicaltrials.gov, NCT04057456 (Not yet recruiting)	2	Spinal Cord Injuries Neuropathic Pain	Placebo diet Anti-inflammatory diet THC/CBD Capsules High CBD Capsules Placebo capsules	Informed consent; SCI >12mo duration; neuropathic pain >3/10 in severity on NRS with average >3/10 pain over the past 7d on screening; ongoing constant pain for >3mo or relapsing/remitting pain for >6mo; dosing of other pain medications stable for >1mo; cannabinoids stopped >7d prior to screening	History of psychotic disorder/convulsive disorder/substance abuse, current SI, intolerance to cannabinoids, traumatic SCI superimposed on prior congenital stenosis; pregnancy; unwilling to stop PRN pain medications; other medical conditions that confound the assessment of neuropathic pain	Average Pain intensity; Sensory Changes; Pain relief	Patient global impression of change; Work productivity and activity; Mood; Depression; Sleep; Spasticity; Pro-inflammatory Biomarkers (IL-2, IL-6, IL-1β, tumor necrosis factor alpha (TNF-α), interferon-gamma (IFN-γ) and prostaglandin E2 (PGE2)); Anti-inflammatory Biomarkers (IL-4, IL-10 and IL-1a)
Effect of Cannabinoids on Spasticity and Neuropathic Pain in Spinal Cord Injured Persons	Clinicaltrials.gov, NCT01222468 (Completed)	2	Muscle Spasticity as a Result of Spinal Cord Injury	Nabilone 0.5mg Placebo	SCI; 12mo post-injury; C2-T12, ASIA A-D, stable level of injury; moderate to severe spasticity or moderate to severe neuropathic pain; no cognitive impairment; medications unchanged for >30d or inadequate pain control at a stabilized dose of gabapentin/pregabalin for >30d; no botulinum toxin injections <6mo	Significant CVS; major illness in another body area; history of psychological disorders or predisposition to psychosis; sensitivity to cannabinoids; severe liver disfunction; history of drug dependency; fixed tendon contractures; used cannabis <30d; unwilling to refrain from smoking cannabis during the study; pregnant or nursing mother	Ashworth Scale; VAS	Spasticity; Sleep; Subject's Global Impression of Change; Clinician's Global Impression of Change; Pain
A Study of Cannabis Based Medicine Extracts and Placebo in Patients with Pain Due to Spinal Cord Injury	Clinicaltrials.gov, NCT01606202 (Completed)	3	Pain	GW-1000-02 (THC 27mg/ml: CBD 25mg/ml) in 100uL Placebo	Informed consent; ≥18yrs; diagnosis of non-acute SCI with central neuropathic pain not wholly relieved by current therapy; central neuropathic pain with mean severity NRS >4 during last 7d of baseline period; stable neurology >6mo; stable medication regimen >4wk; use of contraception during study; no use of cannabinoids >7d, willing to abstain from any use during the study; clinically acceptable laboratory results at visit 2; willingness to comply with all study requirements	History of significant psychiatric disorder other than depression associated with their underlying condition; history of alcohol/substance abuse; severe CVS disorder, (other than atrial fibrillation), poorly controlled htn or severe HF; history of AD, epilepsy; pregnant or nursing mother; significant renal/hepatic impairment; procedures requiring GA during the study; terminal illness; inappropriate for placebo medication; significant disease or disorder in the opinion of the investigator; regular levodopa therapy <7d; known or suspected hypersensitivity/adverse reaction to cannabinoids, intention to travel internationally during the study; intention to donate blood during the study; participation in another research <12wks to study entry; previous randomisation into this study; <18yrs	Mean Central Neuropathic Pain;	Spasticity; Concentration; Quality of Life; Patient Global Impression of Change; Pain; Caregiver Strain; Sleep; Incidence of Adverse Events; Use of Escape Medication

Abbreviations: AD: autonomic dysreflexia; AS: Ashworth Scale; COPD: chronic obstructive pulmonary disease; CVS: cardiovascular disease; d: day; GA: general anesthetic; HF: heart failure; htn: hypertension; IL: interleukin; mo: month; NRS: numerical rating scale, PRN: as needed; SCI: spinal cord injury; SI: suicidal ideation; SZA: schizophrenia; TB: tuberculosis; TBI: traumatic brain injury; wk: week; yrs: year.

severity and evacuation strain, resulted from hemp seed pill use, compared to placebo [101]. Men and women also self-report improved sexual pleasure and satisfaction with cannabinoid use [102], but erectile dysfunction has been observed with men [103]. Furthermore, people with SCI consistently ranked recovery in sexual and bowel/bladder function and reducing cardiovascular complications more importantly than regaining the ability to walk [104]. Thus, the lack of data and the importance of these outcomes to quality of life substantiate the need to include bladder, bowel, sexual function and BP measures in future trials examining the potential of cannabinoids to treat these secondary health issues in people with SCI.

BP should also be routinely monitored among those with cervical and high thoracic SCI due to a decreased capacity of the arterial baroreflex to efficaciously trigger vasoconstriction and maintain BP [105]. OH, a decrease in systolic BP of at least 20 mmHg or diastolic BP of at least 10 mmHg upon postural changes from supine to upright [106], commonly occurs following high-level SCI [105]. OH may lead to dizziness, light-headedness, blurred vision, fatigue, nausea, dyspnea or cognitive deficits [107, 108], and can lead to incapacitation upon the use of cannabinoids [109]. There have been reports that adults with SCI experience lowered BP with cannabinoids [49], which could have profound implications through the exacerbation of existing hypotensive conditions.

Among all the experimental studies, only one (n=20) examined effects of CBD as the main component [58]. Wade *et al*. [58], demonstrated efficacy of THC- and CBD-containing products for pain and spasticity relief, but only CBD-specific products lacked effects of intoxication and decreased concentration. This corroborates findings of studies that have demonstrated the safety of CBD among humans [110]. Moreover, when used in conjunction with THC, CBD may inhibit THC metabolism and decrease THC-related side effects [111]. Therefore, more research needs to be conducted to examine the potential role of CBD as a safer therapeutic agent.

Moreover, all of these studies evaluated symptomatic relief provided by cannabinoids in comparison to placebo. However, greater clinical relevance would be obtained with comparisons to analgesics and anti-spastic medications commonly prescribed to people with SCI.

Another major recommendation for future studies is to investigate chronic cannabinoid use, an area of study that is absent in current research trials. It has been shown in able-bodied individuals that psychotic disorders and cognitive decline may be associated with heavy cannabinoid use [112], which is relevant in people with SCI who often experience significant deficits across cognitive domains such as reasoning, memory, attention, concentration and problem solving [113]. There is also evidence that able-bodied individuals can develop tolerance with long-term cannabinoid use, resulting in decreased side effects and therapeutic effects; therefore, longitudinal studies are warranted [114]. The effects of chronic cannabinoids use across delivery mechanisms on pulmonary function is another pertinent avenue of research in people with SCI, as higher levels of injury are associated with decreased forced vital capacity and forced expired volume [115]. In particular, chronic cannabinoid smoking is associated with dose-related impairments of large airway function resulting in airflow obstruction and hyperinflation [116, 117] and vaporized cannabis, as used in the study by Wilsey *et al*. [60], has been associated with respiratory failure [118].

CONCLUSION

The results of these studies suggest that people with SCI use cannabinoids both recreationally and for its therapeutic effects, primarily for pain and spasticity. The existing evidence also suggests that cannabinoids may help reduce pain and spasticity in people with SCI, at least in the short-term, but the clinical significance and magnitude of its effects appear unclear. Side effects were variable among participants, and were rated as mild to moderate. However, sufficient conclusions cannot be made due to the low quality of evidence and small sample sizes that prevented a meta-analysis. Future studies should be designed as SCI-specific, double-blind RCTs that incorporate larger sample sizes, long-term follow-up, and a wider range of outcomes important to SCI, including BP, bladder, bowel, and sexual function. Moreover, the implementation of standardized outcome measures and cannabinoid formulations, alongside comparisons with traditional therapy, should be utilized to further our understanding of the beneficial and detrimental effects of cannabinoids in people with SCI.

LIST OF ABBREVIATIONS

AD	=	Autonomic Dysreflexia
ALP	=	Alkaline Phosphatase
ALT	=	Alanine Aminotransferase
AS	=	Ashworth Scale
AST	=	Aspartate Aminotransferase
BP	=	Blood Pressure
CBD	=	Cannabidiol
CINAHL	=	Cumulative Index to Nursing and Allied Health Literature
CT-3	=	1',1'-dimethylheptyl-Δ^8-tetrahydrocannabinol-11-oic acid
ECG	=	Electrocardiogram
GPT	=	Grooved Pegboard Test
HR	=	Heart Rate
MAS	=	Modified Ashworth Scale
MCC	=	Maximum Cystometric Capacity
MS	=	Multiple Sclerosis
NIH	=	National Institute of Health
NPP	=	Neuropathic Pain
NRS	=	Numerical Rating Scale

NRSI	=	Non-Randomized Studies of Interventions
OH	=	Orthostatic Hypotension
PRISMA	=	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCTs	=	Randomized Control Trials
RR	=	Respiratory Rate
SCI	=	Spinal Cord Injury
SOMC	=	Short Orientation-Memory-Concentration Test
THC	=	Δ9-tetrahydrocannabinol
TMT	=	Trail-Making Test
VAS	=	Visual Analogue Scale
WAIS-III	=	Weschler Adult Intelligence Scale Digit Symbol Test
γ-GT	=	γ-glutamyl transferase

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

Kylie Nabata – Reports no disclosures. Emmanuel Tse – Reports no disclosures. Amanda Lee – Reports no disclosures. Janice Eng – Reports no disclosures. Matthew Querée – Reports no disclosures. Matthias Walter – Reports no disclosures. Tom Nightingale and Andrei Krassioukov have previously received funding and/or are waiting for decisions on pertinent pending grants from cannabis industry sponsors (Canopy Growth Corporation Ltd and Tetra Bio-Pharma Inc).

ACKNOWLEDGEMENTS

Dr. Krassioukov's laboratory is supported by funds from the Canadian Institute for Health Research, Heart and Stroke Foundation, Canadian Foundation for Innovation and the Craig H. Neilsen Foundation. Emmanuel Tse was a recipient of the 2019 Florence E. Heighway Summer Research Award provided by the UBC Faculty of Medicine. Dr. Nightingale is supported by a 2018-2020 Michael Smith Foundation for Health Research Trainee Award, in conjunction with the International Collaboration on Repair Discoveries (ICORD). Dr. Walter was supported by a 2017-2019 Michael Smith Foundation for Health Research Trainee Award, in partnership with the Rick Hansen Foundation. We would like to acknowledge other members of the Spinal Cord Injury Research Evidence (SCIRE) Team for their support with literature searching and study appraisals. Special thanks to Adam Mesa of ICORD for his work on the graphical abstract.

REFERENCES

[1] Boakye, M.; Leigh, B.C.; Skelly, A.C. Quality of life in persons with spinal cord injury: comparisons with other populations. *J. Neurosurg. Spine,* **2012**, *17*(1)(Suppl.), 29-37. http://dx.doi.org/10.3171/2012.6.AOSPINE1252 PMID: 22985368

[2] Guilcher, S.J.; Craven, B.C.; Lemieux-Charles, L.; Casciaro, T.; McColl, M.A.; Jaglal, S.B. Secondary health conditions and spinal cord injury: an uphill battle in the journey of care. *Disabil. Rehabil.,* **2013**, *35*(11), 894-906. http://dx.doi.org/10.3109/09638288.2012.721048 PMID: 23020250

[3] James, S.L.; Theadom, A.; Ellenbogen, R.G.; Bannick, M.S.; Montjoy-Venning, W.; Lucchesi, L.R.; Abbasi, N.; Abdulkader, R.; Abraha, H.N.; Adsuar, J.C.; Afarideh, M.; Agrawal, S.; Ahmadi, A.; Ahmed, M.B.; Aichour, A.N.; Aichour, I.; Aichour, M.T.E.; Akinyemi, R.O.; Akseer, N.; Alahdab, F.; Alebel, A.; Alghnam, S.A.; Ali, B.A.; Alsharif, U.; Altirkawi, K.; Andrei, C.L.; Anjomshoa, M.; Ansari, H.; Ansha, M.G.; Antonio, C.A.T.; Appiah, S.C.Y.; Ariani, F.; Asefa, N.G.; Asgedom, S.W.; Atique, S.; Awasthi, A.; Ayala Q.B.P.; Ayuk, T.B.; Azzopardi, P.S.; Badali, H.; Badawi, A.; Balalla, S.; Banstola, A.; Barker-Collo, S.L.; Bärnighausen, T.W.; Bedi, N.; Behzadifar, M.; Bekele, B.B.; Belachew, A.B.; Belay, Y.A.; Bennett, D.A.; Bensenor, I.M.; Berhane, A.; Beuran, M.; Bhalla, A.; Bhaumik, S.; Bhutta, Z.A.; Biadgo, B.; Biffino, M.; Bijani, A.; Bililign, N.; Birungi, C.; Boufous, S.; Brazinova, A.; Brown, A.W.; Car, M.; Cárdenas, R.; Carrero, J.J.; Carvalho, F.; Castañeda-Orjuela, C.A.; Catalá-López, F.; Chaiah, Y.; Champs, A.P.; Chang, J-C.; Choi, J-Y.J.; Christopher, D.J.; Cooper, C.; Crowe, C.S.; Dandona, L.; Dandona, R.; Daryani, A.; Davitoiu, D.V.; Degefa, M.G.; Demoz, G.T.; Deribe, K.; Djalalinia, S.; Do, H.P.; Doku, D.T.; Drake, T.M.; Dubey, M.; Dubljanin, E.; El-Khatib, Z.; Ofori-Asenso, R.; Eskandarieh, S.; Esteghamati, A.; Esteghamati, S.; Faro, A.; Farzadfar, F.; Farzaei, M.H.; Fereshtehnejad, S-M.; Fernandes, E.; Feyissa, G.T.; Filip, I.; Fischer, F.; Fukumoto, T.; Ganji, M.; Gankpe, F.G.; Gebre, A.K.; Gebrehiwot, T.T.; Gezae, K.E.; Gopalkrishna, G.; Goulart, A.C.; Haagsma, J.A.; Haj-Mirzaian, A.; Haj-Mirzaian, A.; Hamadeh, R.R.; Hamidi, S.; Haro, J.M.; Hassankhani, H.; Hassen, H.Y.; Havmoeller, R.; Hawley, C.; Hay, S.I.; Hegazy, M.I.; Hendrie, D.; Henok, A.; Hibstu, D.T.; Hoffman, H.J.; Hole, M.K.; Homaie Rad, E.; Hosseini, S.M.; Hostiuc, S.; Hu, G.; Hussen, M.A.; Ilesanmi, O.S.; Irvani, S.S.N.; Jakovljevic, M.; Jayaraman, S.; Jha, R.P.; Jonas, J.B.; Jones, K.M.; Jorjoran S, Z.; Jozwiak, J.J.; Jürisson, M.; Kabir, A.; Kahsay, A.; Kahssay, M.; Kalani, R.; Karch, A.; Kasaeian, A.; Kassa, G.M.; Kassa, T.D.; Kassa, Z.Y.; Kengne, A.P.; Khader, Y.S.; Khafaie, M.A.; Khalid, N.; Khalil, I.; Khan, E.A.; Khan, M.S.; Khang, Y-H.; Khazaie, H.; Khoja, A.T.; Khubchandani, J.; Kiadaliri, A.A.; Kim, D.; Kim, Y-E.; Kisa, A.; Koyanagi, A.; Krohn, K.J.; Defo, K. B.; Kucuk Bicer, B.; Kumar, G. A.; Kumar, M.; Lalloo, R.; Lami, F. H.; Lansingh, V. C.; Laryea, D. O.; Latifi, A.; Leshargie, C. T.; Levi, M.; Li, S.; Liben, M. L.; Lotufo, P. A.; Lunevicius, R.; Mahotra, N. B.; Majdan, M.; Majeed, A.; Malekzadeh, R.; Manda, A.-L.; Mansournia, M. A.; Massenburg, B. B.; Mate, K. K. V.; Mehndiratta, M. M.; Mehta, V.; Meles, H.; Melese, A.; Memiah, P. T. N.; Mendoza, W.; Mengistu, G.; Meretoja, A.; Meretoja, T. J.; Mestrovic, T.; Miazgowski, T.; Miller, T. R.; Mini, G. K.; Mirica, A.; Mirrakhimov, E. M.; Moazen, B.; Mohammadi, M.; Molokhia, M.; Monasta, L.; Mondello, S.; Moosazadeh, M.; Moradi, G.; Moradi, M.; Moradi-Lakeh, M.; Moradinazar, M.; Morrison, S. D.; Moschos, M. M.; Mousavi, S. M.; Murthy, S.; Musa, K. I.; Mustafa, G.; Naghavi, M.; Naik, G.; Najafi, F.; Nangia, V.; Nascimento, B. R.; Negoi, I.; Nguyen, T. H.; Nichols, E.; Ningrum, D. N. A.; Nirayo, Y. L.; Nyasulu, P. S.; Ogbo, F. A.; Oh, I.-H.; Okoro, A.; Olagunju, A. T.; Olagunju, T. O.; Olivares, P. R.; Otstavnov, S. S.; Owolabi, M. O.; P A, M.; Pakhale, S.; Pandey, A. R.; Pesudovs, K.; Pinilla-Monsalve, G. D.; Polinder, S.; Poustchi, H.; Prakash, S.; Qorbani, M.; Radfar, A.; Rafay, A.; Rafiei, A.; Rahimi-Movaghar, A.; Rahimi-Movaghar, V.; Rahman, M.; Rahman, M. A.; Rai, R. K.; Rajati, F.; Ram, U.; Rawaf, D. L.; Rawaf, S.; Reiner, R. C.; Reis, C.; Renzaho, A. M. N.; Resnikoff, S.; Rezaei, S.; Rezaeian, S.; Roever, L.; Ronfani, L.; Roshandel, G.; Roy, N.; Ruhago, G. M.; Saddik, B.; Safari, H.; Safiri, S.; Sahraian, M. A.; Salamati, P.; Saldanha, R. d. F.; Samy, A. M.; Sanabria, J.; Santos, J. V.; Santric Milicevic, M. M. M.; Sartorius, B.; Satpathy, M.; Savuon, K.; Schneider, I. J. C.; Schwebel, D. C.; Sepanlou, S. G.; Shabaninejad, H.; Shaikh, M. A. A.; Shams-Beyranvand, M.; Sharif, M.; Sharif-Alhoseini, M.; Shariful, I. S. M.; She, J.; Sheikh, A.; Shen, J.; Sheth, K. N.; Shibuya, K.; Shiferaw, M. S.; Shigematsu, M.; Shiri, R.; Shiue, I.; Shoman, H.; Siabani, S.; Siddiqi, T. J.; Silva, J. P.; Silveira, D. G. A.; Sinha, D. N.; Smith, M.; Soares, F. A.

M.; Sobhani, S.; Soofi, M.; Soriano, J. B.; Soyiri, I. N.; Stein, D. J.; Stokes, M. A.; Sufiyan, M. a. B.; Sunguya, B. F.; Sunshine, J. E.; Sykes, B. L.; Szoeke, C. E. I.; Tabarés-Seisdedos, R.; Te Ao, B. J.; Tehrani-Banihashemi, A.; Tekle, M. G.; Temsah, M.-H.; Temsah, O.; Topor-Madry, R.; Tortajada-Girbés, M.; Tran, B. X.; Tran, K. B.; Tudor Car, L.; Ukwaja, K. N.; Ullah, I.; Usman, M. S.; Uthman, O. A.; Valdez, P. R.; Vasankari, T. J.; Venketasubramanian, N.; Violante, F. S.; Wagnew, F. W. S.; Waheed, Y.; Wang, Y.-P.; Weldegwergs, K. G.; Werdecker, A.; Wijeratne, T.; Winkler, A. S.; Wyper, G. M. A.; Yano, Y.; Yaseri, M.; Yasin, Y. J.; Ye, P.; Yimer, E. M.; Yip, P.; Yisma, E.; Yonemoto, N.; Yoon, S.-J.; Yost, M. G.; Younis, M. Z.; Yousefifard, M.; Yu, C.; Zaidi, Z.; Zaman, S. B.; Zamani, M.; Zenebe, Z. M.; Zodpey, S.; Feigin, V. L.; Vos, T.; Murray, C. J. L. Global, regional, and national burden of traumatic brain injury and spinal cord injury, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.,* **2019**, *18*(1), 56-87.
http://dx.doi.org/10.1016/S1474-4422(18)30415-0 PMID: 30497965

[4] Brown, A.; Weaver, L.C. The dark side of neuroplasticity. *Exp. Neurol.,* **2012**, *235*(1), 133-141.
http://dx.doi.org/10.1016/j.expneurol.2011.11.004 PMID: 22116043

[5] Bryce, T.N.; Biering-Sørensen, F.; Finnerup, N.B.; Cardenas, D.D.; Defrin, R.; Lundeberg, T.; Norrbrink, C.; Richards, J.S.; Siddall, P.; Stripling, T.; Treede, R.D.; Waxman, S.G.; Widerström-Noga, E.; Yezierski, R.P.; Dijkers, M. International spinal cord injury pain classification: part I. Background and description. March 6-7, 2009. *Spinal Cord,* **2012**, *50*(6), 413-417.
http://dx.doi.org/10.1038/sc.2011.156 PMID: 22182852

[6] Sköld, C.; Levi, R.; Seiger, A. Spasticity after traumatic spinal cord injury: nature, severity, and location. *Arch. Phys. Med. Rehabil.,* **1999**, *80*(12), 1548-1557.
http://dx.doi.org/10.1016/S0003-9993(99)90329-5 PMID: 10597805

[7] Maynard, F.M.; Karunas, R.S.; Waring, W.P., III. Epidemiology of spasticity following traumatic spinal cord injury. *Arch. Phys. Med. Rehabil.,* **1990**, *71*(8), 566-569.
PMID: 2369291

[8] Siddall, P.J.; McClelland, J.M.; Rutkowski, S.B.; Cousins, M.J. A longitudinal study of the prevalence and characteristics of pain in the first 5 years following spinal cord injury. *Pain,* **2003**, *103*(3), 249-257.
http://dx.doi.org/10.1016/S0304-3959(02)00452-9 PMID: 12791431

[9] Holtz, K.A.; Szefer, E.; Noonan, V.K.; Kwon, B.K.; Mills, P.B. Treatment patterns of in-patient spasticity medication use after traumatic spinal cord injury: a prospective cohort study. *Spinal Cord,* **2018**, *56*(12), 1176-1183.
http://dx.doi.org/10.1038/s41393-018-0165-0 PMID: 29904191

[10] Becker, W.J.; Harris, C.J.; Long, M.L.; Ablett, D.P.; Klein, G.M.; DeForge, D.A. Long-term intrathecal baclofen therapy in patients with intractable spasticity. *Can. J. Neurol. Sci.,* **1995**, *22*(3), 208-217.
http://dx.doi.org/10.1017/S031716710003986X PMID: 8529173

[11] Fischer, B.; Ala-Leppilampi, K.; Single, E.; Robins, A. Cannabis law reform in Canada: Is the" Saga of promise, hesitation and retreat" coming to an end? 1. *Can. J. Criminol. Crim. Justice,* **2003**, *45*(3), 265-298.
http://dx.doi.org/10.3138/cjccj.45.3.265

[12] ProCon.org Medical marijuana. Available from: https://medicalmarijuana.procon.org/ (accessed June 25)

[13] Leos-Toro, C.; Shiplo, S.; Hammond, D. Perceived support for medical cannabis use among approved medical cannabis users in Canada. *Drug Alcohol Rev.,* **2018**, *37*(5), 627-636.
http://dx.doi.org/10.1111/dar.12823 PMID: 29873132

[14] Pertwee, R.G. Endocannabinoids and their pharmacological actions. *Handb. Exp. Pharmacol.,* **2015**, *231*, 1-37.
http://dx.doi.org/10.1007/978-3-319-20825-1_1 PMID: 26408156

[15] Small, E.; Cronquist, A. A practical and natural taxonomy for Cannabis. *Taxon,* **1976**, 405-435.
http://dx.doi.org/10.2307/1220524

[16] Mackie, K. Cannabinoid receptors: where they are and what they do. *J. Neuroendocrinol.,* **2008**, *20*(Suppl. 1), 10-14.
http://dx.doi.org/10.1111/j.1365-2826.2008.01671.x PMID: 18426493

[17] Pryce, G.; Baker, D. Control of spasticity in a multiple sclerosis model is mediated by CB1, not CB2, cannabinoid receptors. *Br. J. Pharmacol.,* **2007**, *150*(4), 519-525.
http://dx.doi.org/10.1038/sj.bjp.0707003 PMID: 17220914

[18] Schrot, R.J.; Hubbard, J.R. Cannabinoids: Medical implications. *Ann. Med.,* **2016**, *48*(3), 128-141.
http://dx.doi.org/10.3109/07853890.2016.1145794 PMID: 26912385

[19] Russo, E.B.; Burnett, A.; Hall, B.; Parker, K.K. Agonistic properties of cannabidiol at 5-HT1a receptors. *Neurochem. Res.,* **2005**, *30*(8), 1037-1043.
http://dx.doi.org/10.1007/s11064-005-6978-1 PMID: 16258853

[20] Staton, P.C.; Hatcher, J.P.; Walker, D.J.; Morrison, A.D.; Shapland, E.M.; Hughes, J.P.; Chong, E.; Mander, P.K.; Green, P.J.; Billinton, A.; Fulleylove, M.; Lancaster, H.C.; Smith, J.C.; Bailey, L.T.; Wise, A.; Brown, A.J.; Richardson, J.C.; Chessell, I.P. The putative cannabinoid receptor GPR55 plays a role in mechanical hyperalgesia associated with inflammatory and neuropathic pain. *Pain,* **2008**, *139*(1), 225-236.
http://dx.doi.org/10.1016/j.pain.2008.04.006 PMID: 18502582

[21] Ahrens, J.; Demir, R.; Leuwer, M.; de la Roche, J.; Krampfl, K.; Foadi, N.; Karst, M.; Haeseler, G. The nonpsychotropic cannabinoid cannabidiol modulates and directly activates alpha-1 and alpha-1-Beta glycine receptor function. *Pharmacology,* **2009**, *83*(4), 217-222.
http://dx.doi.org/10.1159/000201556 PMID: 19204413

[22] Burstein, S. Cannabidiol (CBD) and its analogs: a review of their effects on inflammation. *Bioorg. Med. Chem.,* **2015**, *23*(7), 1377-1385.
http://dx.doi.org/10.1016/j.bmc.2015.01.059 PMID: 25703248

[23] De Petrocellis, L.; Ligresti, A.; Moriello, A.S.; Allarà, M.; Bisogno, T.; Petrosino, S.; Stott, C.G.; Di Marzo, V. Effects of cannabinoids and cannabinoid-enriched Cannabis extracts on TRP channels and endocannabinoid metabolic enzymes. *Br. J. Pharmacol.,* **2011**, *163*(7), 1479-1494.
http://dx.doi.org/10.1111/j.1476-5381.2010.01166.x PMID: 21175579

[24] Morales, P.; Hurst, D.P.; Reggio, P.H. Molecular targets of the phytocannabinoids: a complex picture. *Prog. Chem. Org. Nat. Prod.,* **2017**, *103*, 103-131.
http://dx.doi.org/10.1007/978-3-319-45541-9_4 PMID: 28120232

[25] Pernía-Andrade, A.J.; Kato, A.; Witschi, R.; Nyilas, R.; Katona, I.; Freund, T.F.; Watanabe, M.; Filitz, J.; Koppert, W.; Schüttler, J.; Ji, G.; Neugebauer, V.; Marsicano, G.; Lutz, B.; Vanegas, H.; Zeilhofer, H.U. Spinal endocannabinoids and CB1 receptors mediate C-fiber-induced heterosynaptic pain sensitization. *Science,* **2009**, *325*(5941), 760-764.
http://dx.doi.org/10.1126/science.1171870 PMID: 19661434

[26] Ross, R.A. Anandamide and vanilloid TRPV1 receptors. *Br. J. Pharmacol.,* **2003**, *140*(5), 790-801.
http://dx.doi.org/10.1038/sj.bjp.0705467 PMID: 14517174

[27] Hill, K.P.; Palastro, M.D.; Johnson, B.; Ditre, J.W. Cannabis and pain: A clinical review. *Cannabis Cannabinoid Res.,* **2017**, *2*(1), 96-104.
http://dx.doi.org/10.1089/can.2017.0017 PMID: 28861509

[28] Andre, C.M.; Hausman, J.F.; Guerriero, G. *Cannabis sativa*: The plant of the thousand and one molecules. *Front. Plant Sci.,* **2016**, *7*, 19.
http://dx.doi.org/10.3389/fpls.2016.00019 PMID: 26870049

[29] Campbell, F.A.; Tramèr, M.R.; Carroll, D.; Reynolds, D.J.M.; Moore, R.A.; McQuay, H.J. Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review. *BMJ,* **2001**, *323*(7303), 13-16.
http://dx.doi.org/10.1136/bmj.323.7303.13 PMID: 11440935

[30] Gates, P.J.; Albertella, L.; Copeland, J. The effects of cannabinoid administration on sleep: a systematic review of human studies. *Sleep Med. Rev.,* **2014**, *18*(6), 477-487.
http://dx.doi.org/10.1016/j.smrv.2014.02.005 PMID: 24726015

[31] Lynch, M.E.; 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.
http://dx.doi.org/10.1111/j.1365-2125.2011.03970.x PMID: 21426373

[32] Machado, R.F.C.; Stéfano, S.C.; De Cássia, H. R.; Rosa Oliveira, L.M.; Da Silveira, D.X. Therapeutic use of *Cannabis sativa* on chemotherapy-induced nausea and vomiting among cancer patients: systematic review and meta-analysis. *Eur. J. Cancer Care (Engl.),* **2008**, *17*(5), 431-443. http://dx.doi.org/10.1111/j.1365-2354.2008.00917.x PMID: 18625004

[33] Martín-Sánchez, E.; Furukawa, T.A.; Taylor, J.; Martin, J.L.R. Systematic review and meta-analysis of cannabis treatment for chronic pain. *Pain Med.,* **2009**, *10*(8), 1353-1368. http://dx.doi.org/10.1111/j.1526-4637.2009.00703.x PMID: 19732371

[34] Tramèr, M.R.; Carroll, D.; Campbell, F.A.; Reynolds, D.J.M.; Moore, R.A.; McQuay, H.J. Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. *BMJ,* **2001**, *323*(7303), 16-21. http://dx.doi.org/10.1136/bmj.323.7303.16 PMID: 11440936

[35] Higgins, J.; Wells, G. *Cochrane handbook for systematic reviews of interventions.,* **2011**.

[36] Liberati, A.; Altman, D.G.; Tetzlaff, J.; Mulrow, C.; Gøtzsche, P.C.; Ioannidis, J.P.A.; Clarke, M.; Devereaux, P.J.; Kleijnen, J.; Moher, D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med.,* **2009**, *6*(7), e1000100. http://dx.doi.org/10.1371/journal.pmed.1000100 PMID: 19621070

[37] Lung, N. H.; Institute, B. *Study quality assessment tools. 2014,* **2018**.

[38] Sallis, J.F.; Prochaska, J.J.; Taylor, W.C. A review of correlates of physical activity of children and adolescents. *Med. Sci. Sports Exerc.,* **2000**, *32*(5), 963-975. http://dx.doi.org/10.1097/00005768-200005000-00014 PMID: 10795788

[39] Cohen, J. *Statistical power analysis for the behavioral sciences*; Academic press, **2013**. http://dx.doi.org/10.4324/9780203771587

[40] Corey-Bloom, J.; Wolfson, T.; Gamst, A.; Jin, S.; Marcotte, T.D.; Bentley, H.; Gouaux, B. Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial. *CMAJ,* **2012**, *184*(10), 1143-1150. http://dx.doi.org/10.1503/cmaj.110837 PMID: 22586334

[41] Lipsey, M.W.; Wilson, D.B. The efficacy of psychological, educational, and behavioral treatment. Confirmation from meta-analysis. *Am. Psychol.,* **1993**, *48*(12), 1181-1209. http://dx.doi.org/10.1037/0003-066X.48.12.1181 PMID: 8297057

[42] Fekete, C.; Weyers, S.; Siegrist, J.; Michel, G.; Gemperli, A. Poor nutrition and substance use in a Swiss cohort of adults with spinal cord injury. *J. Public Health-Heidelberg,* **2015**, *23*(1), 25-35. http://dx.doi.org/10.1007/s10389-015-0653-z

[43] Young, M.E.; Rintala, D.H.; Rossi, C.D.; Hart, K.A.; Fuhrer, M.J. Alcohol and marijuana use in a community-based sample of persons with spinal cord injury. *Arch. Phys. Med. Rehabil.,* **1995**, *76*(6), 525-532. http://dx.doi.org/10.1016/S0003-9993(95)80506-0 PMID: 7763151

[44] Andresen, S.R.; Biering-Sørensen, F.; Hagen, E.M.; Nielsen, J.F.; Bach, F.W.; Finnerup, N.B. Cannabis use in persons with traumatic spinal cord injury in Denmark. *J. Rehabil. Med.,* **2017**, *49*(2), 152-160. http://dx.doi.org/10.2340/16501977-2105 PMID: 28101559

[45] Drossel, C.; Forchheimer, M.; Meade, M.A. Characteristics of individuals with spinal cord injury who use cannabis for therapeutic purposes. *Top. Spinal Cord Inj. Rehabil.,* **2016**, *22*(1), 3-12. http://dx.doi.org/10.1310/sci2201-3 PMID: 29398889

[46] Aggarwal, S.K.; Carter, G.T.; Sullivan, M.D.; ZumBrunnen, C.; Morrill, R.; Mayer, J.D. Characteristics of patients with chronic pain accessing treatment with medical cannabis in Washington State. *J. Opioid. Manag.,* **2009**, *5*(5), 257-286. http://dx.doi.org/10.5055/jom.2009.0028 PMID: 19947069

[47] Clark, J. M.; Cao, Y.; Krause, J. S. Risk of pain medication misuse after spinal cord injury: the role of substance use, personality, and depression. *J. Pain,,* **2017**, *18*(2), 166-177.

[48] Hwang, M.; Chlan, K.M.; Vogel, L.C.; Zebracki, K. Substance use in young adults with pediatric-onset spinal cord injury. *Spinal Cord,* **2012**, *50*(7), 497-501. http://dx.doi.org/10.1038/sc.2012.8 PMID: 22370762

[49] Hawley, L.A.; Ketchum, J.M.; Morey, C.; Collins, K.; Charlifue, S. Cannabis use in individuals with spinal cord injury or moderate to severe traumatic brain injury in Colorado. *Arch. Phys. Med. Rehabil.,* **2018**, *99*(8), 1584-1590. http://dx.doi.org/10.1016/j.apmr.2018.02.003 PMID: 29524396

[50] Bruce, D.; Brady, J.P.; Foster, E.; Shattell, M. Preferences for medical marijuana over prescription medications among persons living with chronic conditions: Alternative, complementary, and tapering uses. *J. Altern. Complement. Med.,* **2018**, *24*(2), 146-153. http://dx.doi.org/10.1089/acm.2017.0184 PMID: 28945457

[51] Grotenhermen, F.; Schnelle, M. Survey on the medical use of cannabis and THC in Germany. *J. Cannabis Ther.,* **2003**, *3*(2), 17-40. http://dx.doi.org/10.1300/J175v03n02_03

[52] Gorter, R.W.; Butorac, M.; Cobian, E.P.; van der Sluis, W. Medical use of cannabis in the Netherlands. *Neurology,* **2005**, *64*(5), 917-919. http://dx.doi.org/10.1212/01.WNL.0000152845.09088.28 PMID: 15753439

[53] Cardenas, D.D.; Jensen, M.P. Treatments for chronic pain in persons with spinal cord injury: A survey study. *J. Spinal Cord Med.,* **2006**, *29*(2), 109-117. http://dx.doi.org/10.1080/10790268.2006.11753864 PMID: 16739554

[54] Shroff, F.M. Experiences with holistic health practices among adults with spinal cord injury. *Rehabilitation Process and Outcome,* **2015**, *4*, 27-34. http://dx.doi.org/10.4137/RPO.S12363

[55] Hagenbach, U.; Luz, S.; Ghafoor, N.; Berger, J.M.; Grotenhermen, F.; Brenneisen, R.; Mäder, M. The treatment of spasticity with Delta9-tetrahydrocannabinol in persons with spinal cord injury. *Spinal Cord,* **2007**, *45*(8), 551-562. http://dx.doi.org/10.1038/sj.sc.3101982 PMID: 17043680

[56] Karst, M.; Salim, K.; Burstein, S.; Conrad, I.; Hoy, L.; Schneider, U. Analgesic effect of the synthetic cannabinoid CT-3 on chronic neuropathic pain: a randomized controlled trial. *JAMA,* **2003**, *290*(13), 1757-1762. http://dx.doi.org/10.1001/jama.290.13.1757 PMID: 14519710

[57] Rintala, D.H.; Fiess, R.N.; Tan, G.; Holmes, S.A.; Bruel, B.M. Effect of dronabinol on central neuropathic pain after spinal cord injury: a pilot study. *Am. J. Phys. Med. Rehabil.,* **2010**, *89*(10), 840-848. http://dx.doi.org/10.1097/PHM.0b013e3181f1c4ec PMID: 20855984

[58] Wade, D.T.; Robson, P.; House, H.; Makela, P.; Aram, J. A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. *Clin. Rehabil.,* **2003**, *17*(1), 21-29. http://dx.doi.org/10.1191/0269215503cr581oa PMID: 12617376

[59] 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. *Pain,* **2008**, *89*(10), 840-848.

[60] Wilsey, B.; Marcotte, T. D.; 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. *Pain,* **2016**, *17*(9), 982-1000.

[61] Olsen, M.F.; Bjerre, E.; Hansen, M.D.; Tendal, B.; Hilden, J.; Hróbjartsson, A. Minimum clinically important differences in chronic pain vary considerably by baseline pain and methodological factors: systematic review of empirical studies. *J. Clin. Epidemiol.,* **2018**, *101*, 87-106.e2. http://dx.doi.org/10.1016/j.jclinepi.2018.05.007 PMID: 29793007

[62] Lee, J. S.; Hobden, E.; Stiell, I. G.; Wells, G. A. Clinically important change in the visual analog scale after adequate pain control. *Acad. Emerg.,* **2003**, *10*(10), 1128-30.

[63] Dunn, M.; Davis, R. The perceived effects of marijuana on spinal cord injured males. *Paraplegia,* **1974**, *12*(3), 175. PMID: 4453421

[64] Malec, J.; Harvey, R.F.; Cayner, J.J. Cannabis effect on spasticity in spinal cord injury. *Arch. Phys. Med. Rehabil.,* **1982**, *63*(3), 116-118. PMID: 6978699

[65] Heinemann, A.W.; Doll, M.D.; Armstrong, K.J.; Schnoll, S.; Yarkony, G.M. Substance use and receipt of treatment by persons with

long-term spinal cord injuries. *Arch. Phys. Med. Rehabil.,* **1991**, *72*(7), 482-487.
PMID: 2059120

[66] Rothstein, J.L.; Levy, E.; Fecher, R.; Gordon, S.K.; Bauman, W.A. Drug use and abuse in an urban veteran spinal cord injured population. *J. Am. Paraplegia Soc.,* **1992**, *15*(4), 217-220.
http://dx.doi.org/10.1080/01952307.1992.11761521 PMID: 1431868

[67] Kolakowsky-Hayner, S.A.; Gourley, E.V., III; Kreutzer, J.S.; Marwitz, J.H.; Meade, M.A.; Cifu, D.X. Post-injury substance abuse among persons with brain injury and persons with spinal cord injury. *Brain Inj.,* **2002**, *16*(7), 583-592.
http://dx.doi.org/10.1080/02699050110119475 PMID: 12119077

[68] Warms, C.A.; Turner, J.A.; Marshall, H.M.; Cardenas, D.D. Treatments for chronic pain associated with spinal cord injuries: many are tried, few are helpful. *Clin. J. Pain,* **2002**, *18*(3), 154-163.
http://dx.doi.org/10.1097/00002508-200205000-00004 PMID: 12048417

[69] Mahoney, J.S.; Engebretson, J.C.; Cook, K.F.; Hart, K.A.; Robinson-Whelen, S.; Sherwood, A.M. Spasticity experience domains in persons with spinal cord injury. *Arch. Phys. Med. Rehabil.,* **2007**, *88*(3), 287-294.
http://dx.doi.org/10.1016/j.apmr.2006.12.029 PMID: 17321818

[70] Heutink, M.; Post, M.W.; Wollaars, M.M.; van Asbeck, F.W. Chronic spinal cord injury pain: pharmacological and non-pharmacological treatments and treatment effectiveness. *Disabil. Rehabil.,* **2011**, *33*(5), 433-440.
http://dx.doi.org/10.3109/09638288.2010.498557 PMID: 20695788

[71] Patel, T.; Milligan, J.; Lee, J. Medication-related problems in individuals with spinal cord injury in a primary care-based clinic. *J. Spinal Cord Med.,* **2017**, *40*(1), 54-61.
http://dx.doi.org/10.1179/2045772315Y.0000000055 PMID: 26446538

[72] Bourke, J.A.; Catherwood, V.J.; Nunnerley, J.L.; Martin, R.A.; Levack, W.M.M.; Thompson, B.L.; Acland, R.H. Using cannabis for pain management after spinal cord injury: a qualitative study. *Spinal Cord Ser. Cases,* **2019**, *5*, 82.
http://dx.doi.org/10.1038/s41394-019-0227-3 PMID: 31632740

[73] Eldridge, L.A.; Piatt, J.A.; Agley, J.; Gerke, S. Relationship between substance use and the onset of Spinal Cord Injuries: A medical chart review. *Top. Spinal Cord Inj. Rehabil.,* **2019**, *25*(4), 316-321.
http://dx.doi.org/10.1310/sci2504-316 PMID: 31844383

[74] Graupensperger, S.; Corey, J.J.; Turrisi, R.J.; Evans, M.B. Individuals with spinal cord injury have greater odds of substance use disorders than non-sci comparisons. *Drug Alcohol Depend.,* **2019**, *205,* 107608.
http://dx.doi.org/10.1016/j.drugalcdep.2019.107608 PMID: 31606588

[75] Stillman, M.; Capron, M.; Mallow, M.; Ransom, T.; Gustafson, K.; Bell, A.; Graves, D. Utilization of medicinal cannabis for pain by individuals with spinal cord injury. *Spinal Cord Ser. Cases,* **2019**, *5*, 66.
http://dx.doi.org/10.1038/s41394-019-0208-6 PMID: 31632724

[76] Kogel, R.W.; Johnson, P.B.; Chintam, R.; Robinson, C.J.; Nemchausky, B.A. Treatment of spasticity in spinal cord injury with dronabinol, a tetrahydrocannabinol derivative. *Am. J. Ther.,* **1995**, *2*(10), 799-805.
http://dx.doi.org/10.1097/00045391-199510000-00012 PMID: 11854790

[77] Pooyania, S.; Ethans, K.; Szturm, T.; Casey, A.; Perry, D. A randomized, double-blinded, crossover pilot study assessing the effect of nabilone on spasticity in persons with spinal cord injury. *Arch. Phys. Med. Rehabil.,* **2010**, *91*(5), 703-707.
http://dx.doi.org/10.1016/j.apmr.2009.12.025 PMID: 20434606

[78] Shaw, L.; Rodgers, H.; Price, C.; van Wijck, F.; Shackley, P.; Steen, N.; Barnes, M.; Ford, G.; Graham, L. BoTULS investigators. BoTULS: a multicentre randomised controlled trial to evaluate the clinical effectiveness and cost-effectiveness of treating upper limb spasticity due to stroke with botulinum toxin type A. *Health Technol. Assess.,* **2010**, *14*(26), 1-113, iii-iv.
http://dx.doi.org/10.3310/hta14260 PMID: 20515600

[79] Meseguer-Henarejos, A.B.; Sánchez-Meca, J.; López-Pina, J.A.; Carles-Hernández, R. Inter- and intra-rater reliability of the modified ashworth scale: a systematic review and meta-analysis. *Eur. J. Phys. Rehabil. Med.,* **2018**, *54*(4), 576-590.
PMID: 28901119

[80] Degenhardt, L.; Hall, W.; Lynskey, M. Exploring the association between cannabis use and depression. *Addiction,* **2003**, *98*(11), 1493-1504.
http://dx.doi.org/10.1046/j.1360-0443.2003.00437.x PMID: 14616175

[81] Lee, M.C.; Ploner, M.; Wiech, K.; Bingel, U.; Wanigasekera, V.; Brooks, J.; Menon, D.K.; Tracey, I. Amygdala activity contributes to the dissociative effect of cannabis on pain perception. *Pain,* **2013**, *154*(1), 124-134.
http://dx.doi.org/10.1016/j.pain.2012.09.017 PMID: 23273106

[82] Weizman, L.; Dayan, L.; Brill, S.; Nahman-Averbuch, H.; Hendler, T.; Jacob, G.; Sharon, H. Cannabis analgesia in chronic neuropathic pain is associated with altered brain connectivity. *Neurology,* **2018**, *91*(14), e1285-e1294.
http://dx.doi.org/10.1212/WNL.0000000000006293 PMID: 30185448

[83] Krassioukov, A.; Eng, J.J.; Warburton, D.E.; Teasell, R. Spinal cord injury rehabilitation evidence research team. A systematic review of the management of orthostatic hypotension after spinal cord injury. *Arch. Phys. Med. Rehabil.,* **2009**, *90*(5), 876-885.
http://dx.doi.org/10.1016/j.apmr.2009.01.009 PMID: 19406310

[84] Barbonetti, A.; Caterina Vassallo, M.R.; Cotugno, M.; Felzani, G.; Francavilla, S.; Francavilla, F. Low testosterone and non-alcoholic fatty liver disease: Evidence for their independent association in men with chronic spinal cord injury. *J. Spinal Cord Med.,* **2016**, *39*(4), 443-449.
http://dx.doi.org/10.1179/2045772314Y.0000000288 PMID: 25614040

[85] Borini, P.; Guimarães, R.C.; Borini, S.B. Possible hepatotoxicity of chronic marijuana usage. *Sao Paulo Med. J.,* **2004**, *122*(3), 110-116.
http://dx.doi.org/10.1590/S1516-31802004000300007 PMID: 15448809

[86] Adejumo, A.C.; Alliu, S.; Ajayi, T.O.; Adejumo, K.L.; Adegbala, O.M.; Onyeakusi, N.E.; Akinjero, A.M.; Durojaiye, M.; Bukong, T.N. Cannabis use is associated with reduced prevalence of non-alcoholic fatty liver disease: A cross-sectional study. *PLoS One,* **2017**, *12*(4), e0176416.
http://dx.doi.org/10.1371/journal.pone.0176416 PMID: 28441459

[87] National Academies of Sciences. *E.; Medicine, The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research*; National Academies Press, **2017**.

[88] Hagen, E.M.; Rekand, T. Management of Neuropathic Pain Associated with Spinal Cord Injury. *Pain Ther.,* **2015**, *4*(1), 51-65.
http://dx.doi.org/10.1007/s40122-015-0033-y PMID: 25744501

[89] Russo, E.B. The case for the entourage effect and conventional breeding of clinical cannabis: No "Strain," No Gain. *Front. Plant Sci.,* **2019**, *9*, 1969.
http://dx.doi.org/10.3389/fpls.2018.01969 PMID: 30687364

[90] Cooper, Z. D.; Bedi, G.; Ramesh, D.; Balter, R.; Comer, S. D.; Haney, M. Impact of co-administration of oxycodone and smoked cannabis on analgesia and abuse liability. *Neuropsychopharmacology,* **2018**, *43*(10), 2046-2055.

[91] Bachhuber, M.A.; Saloner, B.; Cunningham, C.O.; Barry, C.L. Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010. *JAMA Intern. Med.,* **2014**, *174*(10), 1668-1673.
http://dx.doi.org/10.1001/jamainternmed.2014.4005 PMID: 25154332

[92] Stewart, L.; Moher, D.; Shekelle, P. Why prospective registration of systematic reviews makes sense. *Syst. Rev.,* **2012**, *1*, 7-7.
http://dx.doi.org/10.1186/2046-4053-1-7 PMID: 22588008

[93] Schöps, T.F.; Schneider, M.P.; Steffen, F.; Ineichen, B.V.; Mehnert, U.; Kessler, T.M. Neurogenic lower urinary tract dysfunction (NLUTD) in patients with spinal cord injury: long-term urodynamic findings. *BJU Int.,* **2015**, *115*(Suppl. 6), 33-38.
http://dx.doi.org/10.1111/bju.13085 PMID: 25891318

[94] Fowler, C.J.; Griffiths, D.; de Groat, W.C. The neural control of micturition. *Nat. Rev. Neurosci.,* **2008**, *9*(6), 453-466.
http://dx.doi.org/10.1038/nrn2401 PMID: 18490916

[95] Wan, D.; Krassioukov, A.V. Life-threatening outcomes associated with autonomic dysreflexia: a clinical review. *J. Spinal Cord Med.,* **2014**, *37*(1), 2-10.
http://dx.doi.org/10.1179/2045772313Y.0000000098 PMID: 24090418

[96] Krassioukov, A.; Warburton, D.E.; Teasell, R.; Eng, J.J. Spinal cord injury rehabilitation evidence research team. A systematic review of the management of autonomic dysreflexia after spinal cord injury. *Arch. Phys. Med. Rehabil.,* **2009**, *90*(4), 682-695. http://dx.doi.org/10.1016/j.apmr.2008.10.017 PMID: 19345787

[97] Salaga, M.; Abalo, R.; Fichna, J. Cannabis and cannabinoids and the effects on gastrointestinal function: an overview. *Handbook of Cannabis and Related Pathologies: Biology, Pharmacology, Diagnosis, and Treatment*; Preedy, V.R., Ed.; Academic Print, **2017**, pp. 471-480. http://dx.doi.org/10.1016/B978-0-12-800756-3.00056-9

[98] Hedlund, P. Cannabinoids and the endocannabinoid system in lower urinary tract function and dysfunction. *Neurourol. Urodyn.,* **2014**, *33*(1), 46-53. http://dx.doi.org/10.1002/nau.22442 PMID: 24285567

[99] Freeman, R.M.; Adekanmi, O.; Waterfield, M.R.; Waterfield, A.E.; Wright, D.; Zajicek, J. The effect of cannabis on urge incontinence in patients with multiple sclerosis: a multicentre, randomised placebo-controlled trial (CAMS-LUTS). *Int. Urogynecol. J. Pelvic Floor Dysfunct.,* **2006**, *17*(6), 636-641. http://dx.doi.org/10.1007/s00192-006-0086-x PMID: 16552618

[100] Brady, C.M.; DasGupta, R.; Dalton, C.; Wiseman, O.J.; Berkley, K.J.; Fowler, C.J. An open-label pilot study of cannabis-based extracts for bladder dysfunction in advanced multiple sclerosis. *Mult. Scler.,* **2004**, *10*(4), 425-433. http://dx.doi.org/10.1191/1352458504ms1063oa PMID: 15327041

[101] Cheng, C.W.; Bian, Z.X.; Zhu, L.X.; Wu, J.C.; Sung, J.J. Efficacy of a Chinese herbal proprietary medicine (Hemp Seed Pill) for functional constipation. *Am. J. Gastroenterol.,* **2011**, *106*(1), 120-129. http://dx.doi.org/10.1038/ajg.2010.305 PMID: 21045817

[102] Halikas, J.; Weller, R.; Morse, C. Effects of regular marijuana use on sexual performance. *J. Psychoactive Drugs,* **1982**, *14*(1-2), 59-70. http://dx.doi.org/10.1080/02791072.1982.10471911 PMID: 6981694

[103] Cohen, S. Cannabis and sex: multifaceted paradoxes. *J. Psychoactive Drugs,* **1982**, *14*(1-2), 55-58. http://dx.doi.org/10.1080/02791072.1982.10471910 PMID: 7119944

[104] Anderson, K.D. Targeting recovery: priorities of the spinal cord-injured population. *J. Neurotrauma,* **2004**, *21*(10), 1371-1383. http://dx.doi.org/10.1089/neu.2004.21.1371 PMID: 15672628

[105] Claydon, V.E.; Steeves, J.D.; Krassioukov, A. Orthostatic hypotension following spinal cord injury: understanding clinical pathophysiology. *Spinal Cord,* **2006**, *44*(6), 341-351. http://dx.doi.org/10.1038/sj.sc.3101855 PMID: 16304564

[106] The Consensus Committee of the American Autonomic Society and the American Academy of Neurology. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. *Neurology,* **1996**, *46*(5), 1470. http://dx.doi.org/10.1212/WNL.46.5.1470 PMID: 8628505

[107] Freeman, R.; Abuzinadah, A.R.; Gibbons, C.; Jones, P.; Miglis, M.G.; Sinn, D.I. Orthostatic hypotension: JACC State-of-the-Art review. *J. Am. Coll. Cardiol.,* **2018**, *72*(11), 1294-1309. http://dx.doi.org/10.1016/j.jacc.2018.05.079 PMID: 30190008

[108] Mathias, C.J. Orthostatic hypotension and paroxysmal hypertension in humans with high spinal cord injury. *Prog. Brain Res.,* **2006**, *152*, 231-243. http://dx.doi.org/10.1016/S0079-6123(05)52015-6 PMID: 16198704

[109] Jones, R.T. Cardiovascular system effects of marijuana. *J. Clin. Pharmacol.,* **2002**, *42*(S1), 58S-63S. http://dx.doi.org/10.1002/j.1552-4604.2002.tb06004.x PMID: 12412837

[110] Bergamaschi, M.M.; Queiroz, R.H.; Zuardi, A.W.; Crippa, J.A. Safety and side effects of cannabidiol, a *Cannabis sativa* constituent. *Curr. Drug Saf.,* **2011**, *6*(4), 237-249. http://dx.doi.org/10.2174/157488611798280924 PMID: 22129319

[111] Huestis, M.A. Human cannabinoid pharmacokinetics. *Chem. Biodivers.,* **2007**, *4*(8), 1770-1804. http://dx.doi.org/10.1002/cbdv.200790152 PMID: 17712819

[112] Bolla, K.I.; Brown, K.; Eldreth, D.; Tate, K.; Cadet, J.L. Dose-related neurocognitive effects of marijuana use. *Neurology,* **2002**, *59*(9), 1337-1343. http://dx.doi.org/10.1212/01.WNL.0000031422.66442.49 PMID: 12427880

[113] Sachdeva, R.; Gao, F.; Chan, C.C.H.; Krassioukov, A.V. Cognitive function after spinal cord injury: A systematic review. *Neurology,* **2018**, *91*(13), 611-621. http://dx.doi.org/10.1212/WNL.0000000000006244 PMID: 30158159

[114] Jones, R.T.; Benowitz, N.; Bachman, J. Clinical studies of cannabis tolerance and dependence. *Ann. N. Y. Acad. Sci.,* **1976**, *282*(1), 221-239. http://dx.doi.org/10.1111/j.1749-6632.1976.tb49901.x PMID: 798533

[115] Linn, W.S.; Adkins, R.H.; Gong, H., Jr; Waters, R.L. Pulmonary function in chronic spinal cord injury: a cross-sectional survey of 222 southern California adult outpatients. *Arch. Phys. Med. Rehabil.,* **2000**, *81*(6), 757-763. http://dx.doi.org/10.1016/S0003-9993(00)90107-2 PMID: 10857520

[116] Jett, J.; Stone, E.; Warren, G.; Cummings, K.M. Cannabis use, lung cancer, and related issues. *J. Thorac. Oncol.,* **2018**, *13*(4), 480-487. http://dx.doi.org/10.1016/j.jtho.2017.12.013 PMID: 29374567

[117] Aldington, S.; Williams, M.; Nowitz, M.; Weatherall, M.; Pritchard, A.; McNaughton, A.; Robinson, G.; Beasley, R. Effects of cannabis on pulmonary structure, function and symptoms. *Thorax,* **2007**, *62*(12), 1058-1063. http://dx.doi.org/10.1136/thx.2006.077081 PMID: 17666437

[118] Dicpinigaitis, P.V.; Trachuk, P.; Fakier, F.; Teka, M.; Suhrland, M.J. Vaping-Associated acute respiratory failure due to acute lipoid pneumonia. *Lung,* **2019**, *198*(1),31-33. PMID: 31583455