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Cannabinoids in Spinal Cord Injury

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Key Points

- Cannabis is a plant that contains cannabinoids, which are agents that act on the endocannabinoid system; an ancient, evolutionary conserved system that regulates our bodies in many ways, most of them still poorly understood.
- Legal cannabis production, use, and distribution for medical and recreational use is regulated in Canada. Production, distribution and use of synthetic forms of cannabis are highly regulated and approved for medical uses only. In many parts of the world recreational and/or medical use of cannabis may be illegal or restricted.
- THC and CBD are two common cannabinoids. THC is psychoactive, and though CBD is not, it seems to modulate the psychoactive effects of THC.
- Cannabis may be inhaled, ingested, or applied topically. The effects and risks vary depending on the mode of administration, the cannabis type, amount, and dosage.
- Current scientific literature is insufficient to inform specific dose regimens for SCI and for most other conditions.
- Cannabis may have a small positive effect on pain and spasticity management in people with SCI.
- Quality of evidence on other effects of cannabis in non-SCI populations limits generalizability or application of findings
- Most short-term side effects are mild to moderate and dose dependent.
- Dry mouth, fatigue, and hunger are the most common side effects in the SCI population.
- Autonomic, cardiovascular, and respiratory side effects may not be common in SCI patients using cannabis, but more research is needed.
- Where autonomic, cardiovascular, and respiratory functions are important prognostic factors, people with SCI who use cannabis should be regularly monitored for changes in these functions.
- Cannabis use may lead to depressive and anxious symptoms, though these are not commonly reported by SCI patients in studies conducted to date.
- Long term use of cannabis is associated with tolerance, dependence, and symptoms of withdrawal when discontinued. Lifetime risk of developing cannabis dependence syndrome has been documented as 9% for cannabis users in general.
- Long term use of cannabis is associated with chronic psychotic illness with younger adults, though causality is unclear.
- Naïve cannabis users may experience acute intoxication symptoms including feelings of anxiety and panic, combined with nausea, vomiting, or fainting as well as symptoms of misperception and distortion of time and space.

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1 What is Cannabis?

Cannabis is a term that refers to the products of cannabis (hemp) plants, a group of plants from central Asia that are now cultivated around the world. *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis* are three well known types of cannabis, but many strains or varieties exist, including pure and hybrid types. Common preparations of cannabis include marijuana, which is the dried leaves and flowering tops of the plant, and hashish, which is its condensed resin. Cannabis has been used for thousands of years as a medicine and as a recreational drug (Atakan, 2012).

Cannabis is a controlled substance in most regions of the world because of its psychoactive effects (Habibi et al. 2018). In some regions, cannabis is approved for medical or spiritual uses only. Dried cannabis and oil were made legal in Canada for recreational purposes in October 2018 (Cannabis Act, 2018); and edibles and concentrates (e.g., foods, oils, tinctures) were made legal and available through authorized vendors in October 2019.

1.1 How Does Cannabis Work?

Cannabis is a plant that contains cannabinoids, which are agents that act on the endocannabinoid system; an ancient, evolutionary conserved system that regulates our bodies in many ways, most of them still poorly understood (Rodriguez et al. 2005). Cannabinoids occur naturally in cannabis plants (*phytocannabinoids*) but can also be synthesized in a lab (*synthetic cannabinoids*). Synthetic cannabis must be approved by Health Canada (or other governing agency) and prescribed by a physician to ensure quality control (Health Canada, 2018). For example, cannabis grown through licensed vendors is regulated in Canada to ensure safe agricultural practices, and cannabinoid concentrations (Health Canada, 2016).

There are more than 60 cannabinoids present in cannabis. Commonly known as THC, *Delta-9-tetrahydrocannabinol* is possibly the most well-known, and is responsible for many of the psychoactive effects, such as creating a "high" or sense of euphoria. *Cannabidiol* (CBD) is a primary non-psychoactive cannabinoid that plays an important role in modulating the psychoactive effects of THC. The mechanism of action of CBD is not completely clear, but it seems that CBD has similar effects to THC in some domains (e.g., potential antiemetic, anti-inflammatory, and immunomodulatory properties) and opposite effects in others (e.g., potential antipsychotic and sedating properties: Atakan, 2012). Most of these effects are dependent on dose, and the ratio of THC to CBD. High THC to low CBD ratio products tend to have a stronger psychoactive effect in comparison to those with more balanced ratios (i.e., 1:1; Atakan, 2012). However, there is a tipping point, where the psychoactive effects of THC are enhanced in higher absolute CBD doses (Atakan, 2012).

1.2 Modes of Administration

Cannabis may be inhaled, ingested, or (less commonly) applied topically, rectally, or intravenously. The risks associated with smoking cannabis are like smoking tobacco (Health Canada, 2018). Smoking with a vaporizer distributes fewer toxic substances to the lungs, but it is

associated with the risk of vaping-associated pulmonary injury (Werner et al., 2020). The additive Vitamin E acetate is strongly associated with vape injury, but there may be contribution of other chemicals (Werner et al., 2020). The issue with edibles, oils, concentrates, and drinks is that they have varying doses of THC and if not regulated, may contain toxic by-products (e.g., mold, bacteria, pesticides and traces of heavy metals: McPartland, 2017). This risk is thought to be significantly lower in products from governmental sources, due to stringent quality control measures. Cannabinoids are usually taken through inhalation or orally; other routes of administration such as rectally, sublingual administration, transdermal administration, eye drops and aerosols are rarely studied and of little relevance (Bridgeman and Abazia, 2017). All routes of administration, such as orally, rectally, and parenterally, are free of the risk of chronic inflammatory disease and upper respiratory cancer. Topically, THC is not well absorbed through the skin, thus the time of onset and duration of action are unknown. There are some reports of rash and itching when the skin comes into contact with cannabis products (Manini et al., 2015).

The cannabinoid type, administration route, and concentration are separate factors that together account for the effects it has on the body. Inhaling cannabis makes it act faster than ingesting it, but the duration of effect is shorter. There is no standard cannabis dosing regimen for people with SCI. Experienced users who use cannabis for medical purposes reported using 1-3 g/day (Health Canada, 2018). Generally, products containing only THC tend to have a stronger psychoactive effect than products containing THC and CBD in equal concentrations. Oil containing only CBD has no psychoactive effects. Products containing only CBD are taken for a range of ailments, but there is limited safety and efficacy data and no research in SCI. People who have never used cannabis tend to experience more side effects and are advised to start with low doses and select a high CBD to relatively low THC concentration product (Health Canada, 2018).

2 What are Cannabinoids Used for in Spinal Cord Injury?

Cannabinoids are a potential new treatment for post-SCI pain in need of further study. Preliminary results from a pilot (N=5) randomized controlled trial on dronabinol (synthetic THC) suggest that it is not effective in reducing neuropathic pain post-SCI (Rintala et al. 2010). Ultramicronized palmitoylethanolamide (Normast), a laboratory made form of an endocannabinoid that occurs naturally in the human body, was shown to not be effective in reducing chronic pain post-SCI (Andresen et al. 2016). Nabilone (a standardized synthetic THC cannabis plant product in tablet form) and 2.9% THC vapor have been shown to be effective in reducing spasticity, and dronabinol may help reduce spasticity (Pooyania et al. 2010).

People with SCI report using cannabis for pain, spasticity, and pleasure, feelings of anxiety, stress, and depression, bowel and bladder impairment, nausea, loss of appetite, sleep disturbance; and to decrease use of other prescription medications, as well as using cannabis for pleasure, recreation and relaxation (Nabata et al. 2020; Cardenas & Jensen, 2006; Shroff, 2015; Drossel et al. 2016; Andresen et al. 2017, Bruce et al. 2018, Hawley et al. 2018). However, observational studies have only demonstrated effects on pain and spasticity and results to date

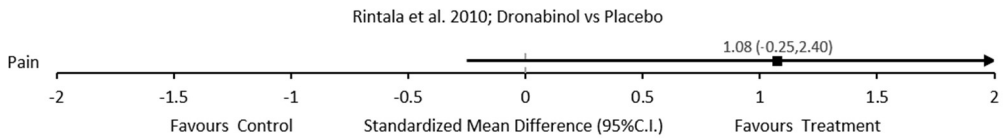
are preliminary and only demonstrate the potential of its effectiveness. No meta-analyses could be performed and there are no best practice recommendations for dose because all studies found used different cannabis products and dose regimens.

2.1 Pain

Table 1. Pain, Cannabinoids and SCI

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Andresen et al. 2016 Denmark RCT PEDro = 11 Level 1 N=73	**Population**: Mean age=56.3±11.6 yr; Gender: males=54, females=19; Time since injury=10.3±11.7 yr; Level of injury: tetraplegia=32, paraplegia=41; Severity of injury: AIS A=24, B=3, C=15, D=31; Type of pain=neuropathic. **Intervention**: Participants were randomized to a ultramicronized palmitoylethanolamide (Normast) group or a placebo group taking dosages 2 times daily with 12 h between dosages, for 12 wks. **Outcome Measures:** Numeric Rating scale (0-10) for change in neuropathic pain intensity from baseline wk to wk 12. Secondary outcomes: analysis and effects on spasticity, evoked pain, sleep problems, anxiety, depression and global impression of change.	1. No significant difference between change in neuropathic pain intensity observed between the Normast and placebo groups (p=0.46). 2. No significant difference over time between the two groups when using covariates (p=0.82). 3. Normast group had a significant reduction in their use of rescue medication compared to the placebo group (p=0.02). 4. Normast group showed a significant increase in intensity of spasticity observed in the pain diary recordings compared to a decrease in the placebo group (p=0.013). 5. No significant differences observed in any of the other outcome measures (p>0.05).
Wilsey et al. 2016 USA RCT Crossover PEDro=8 Level 1 N=42 (29 SCI)	**Population**: Mean age=46.4±13.6 yr; gender: males=29, females=13; Level of injury: C=22, T=14, L=6. Intervention: crossover design with placebo, 2.9% and 6.7% THC vapour; 4 puffs at t=0 and 4 puffs at t = 240 min. Treatment periods were 480 min. for each exposure with measurements every 60 min. **Outcome Measures**: 11-point pain scale, Patient Global Impression of	1. 2.9% THC group (2nd dose at t = 240 min.): a. Pain intensity was significantly reduced at all measurement points (p<0.05, a t = 120/240 min. <0.01). b. Pain relief was significantly higher at all measurement points (p<0.0001) except 360 minutes.

	Change, Neuropathic Pain Scale, VAS allodynia, Heat-pain threshold.	c. All neuropathic pain measures improved except itching at all measurement points (p<0.0001). 2. 6.7% THC group (2nd dose at t = 240 min.): a. Pain intensity was significantly reduced at t = 60, t = 300, t = 360 and t = 420 min. (p<0.05). b. Pain relief was significantly higher at all measurement points (p<0.0001). c. All neuropathic pain measures improved except itching at all measurement points (p<0.0001).
Rintala et al. 2010 USA Crossover-RCT PEDro=5 Level 2 N=5	**Population:** Convenience sample. Mean age: 50.1 yr; Level of injury: paraplegia=4, tetraplegia=3; Level of severity: AIS A=4, B=1, D=2; Mean time since injury: 21.9 yr; Type of pain: neuropathic (>6 months) **Intervention:** Participants were randomized into two groups: i) 5 mg dronabinol titrated every third day (max 20 mg/day); ii) 25 mg diphenhydramine day once then titrated up to 75 mg/day. Participants remained in a 7 day stabilization phase once titration was complete and then a 28 day maintenance phase. After a 9 day down-titration period and 7 day washout period, participants crossed over to the other arm. Participants stopped all pain medication prior to the study and were allowed break-through medication during the study, consisting of 5mg/325mg oxycodone/acetaminophen max. 8d./24h. **Outcome Measures:** Brief Pain Inventory (BPI).	1. Pain intensity was not significantly different between the dronabinol and diphenhydramine groups. (n=5) 2. Seven people started the study, but 2 participants dropped out during the first round while in the Dronabinol group, one participant due to side-effects and the other unwilling to stop taking dronabinol. 3. 3 participants used break-through medication during the study. Their patterns of use were occasionally, 2 tablets daily and 8 tablets daily. 4. No significant difference was seen in side effects between the groups. 5. Most common side effects included dry mouth, constipation, fatigue and drowsiness.
	Effect Sizes: Forest plot of standardized mean differences (SMD±95%C.I.) as calculated from pre- and post-intervention data.	

		
Hagenbach et al. 2007 Switzerland Phase 1 Open-label Clinical Trial N=15 RCT PEDro=4 Level 2 N=13	**Population:** SCI (N=15): Age range: 29-66 yr; Gender: males=11, females=2; Level of injury: C4-T11; Level of severity: AIS A,B,C,D; Type of pain: spastic. **Intervention:** Phase 1-2: Patients received 10 mg oral tetrahydrocannabinol (THC) on day one. Dose titration began on day two until the maximum tolerated dose or treatment aim was achieved and maintained for 6 wk. Phase 3: In a double-blind design, SCI patients from phase 1 of the study were randomly assigned to either maximum oral THC doses (6 participants) or placebo doses (7 participants) for 6 wk. **Outcome Measures:** Self ratings.	1. Mean average tolerated dose was 31 mg/day orally and 43 mg/day rectally delivered THC. 2. Significant improvement in pain was seen on day one compared to baseline measures (p=0.047). 3. No significant improvement in pain was seen compared to placebo on day 8 and 43. 4. Individuals in the oral THC group showed no significant difference in mood or attention compared to the placebo group or to baseline. 5. Total of 9 dropouts during open-label phases were due to increased pain, anxiety, decreased compliance, decreased attention and mood.

Discussion

Four randomized-controlled trials examined the effects of cannabinoids for pain in SCI; one study found that cannabinoids significantly reduced pain, two studies found no significant difference in pain reduction between cannabinoids and placebo and in the fourth study the RCT analysis of the primary outcome measure was not possible due to the high drop-out rate, the open-label part showed a significant reduction in pain.

Wilsey et al. (2016) found cannabis vapor significantly reduced pain post-SCI compared to placebo vapor. Rintala et al. (2010) examined the effect of dronabinol versus an active control (diphenhydramine) on neuropathic pain post-SCI in a small pilot RCT (n=5). They had two dropouts during the first phase of the study: one participant dropped out while on dronabinol due to side effects and the other participant on dronabinol did not want to stop medication for wash-out phase. The study found no significant difference in pain intensity between the two treatments in the 5 participants who completed the full trial. In addition to the small size of the RCT, limitations include the use of convenience sampling and use of two different baseline measures: the end of week 1 for phase 1 versus the end of wash-out for phase 2.

Hagenbach et al. (2007) conducted a study primarily examining the effectiveness of THC in improving spasticity and secondarily, in improving spastic pain in people with SCI. In the first phase of the study, 22 participants received 10mg of oral THC which was then dose titrated until

maximum tolerance or treatment dose was reached for 6 weeks. The main analysis of the RCT part of the study was not possible due to the high dropout rate. In the open-label phase they found a significant reduction in pain of people with SCI post treatment (p=0.047). There was no significant reduction of pain compared to placebo on day 8 and 43 when comparing the intervention group of open-label part of the study to the placebo group in the RCT part of the study. Four patients noted pain relief (18%), but five (23%) reported pain augmentation and four dropped out: pain was one of the major reasons for the high dropout rate. We assign it a lower level of evidence (i.e., level 2) than would be expected of an RCT (i.e., PEDro≥6 RCT).

Andresen et al. 2016 did an RCT on the effects of the endocannabinoid palmitoylethanolamide (PEA), marketed in ultramicronized form as Normast. They administered it or a placebo twice a day with 12 hours between dosages for 12 weeks. Using a numeric rating scale from 0 to 10, they found no significant difference in neuropathic pain intensity between the two groups (p=0.46).

Conclusion

There is level 1b evidence (Wilsey et al. 2016) that natural cannabis vapour improves neuropathic pain post- SCI.

There is level 1b evidence (Andresen et al. 2016) that ultramicronized Palmitoylethanolamide (PEA/Normast) does not significantly improve chronic neuropathic pain post-SCI.

There is level 2 evidence (from one randomized-controlled crossover pilot trial; Rintala et al. 2010) that synthetic dronabinol may not be effective in reducing neuropathic pain intensity post SCI.

There is conflicting level 2 evidence (from one randomized controlled trial; Hagenbach et al. 2007) for the use of synthetic delta-9-tetra hydrocannabinol in reducing spastic pain in SCI individuals.

Key Points

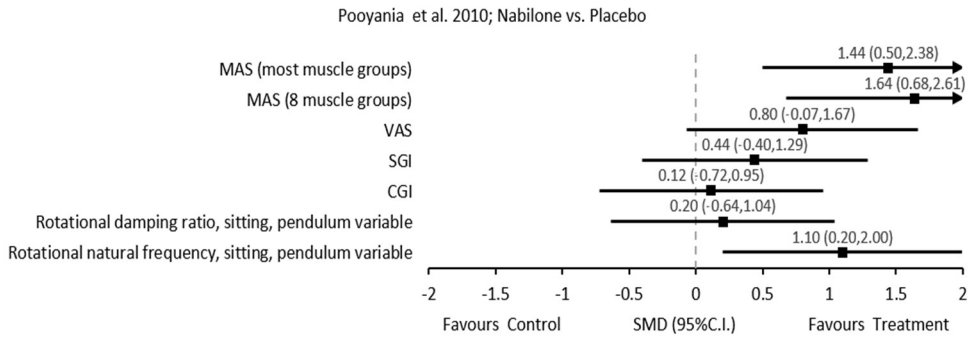
Cannabinoids are a potential treatment for post-SCI pain in need of further study.

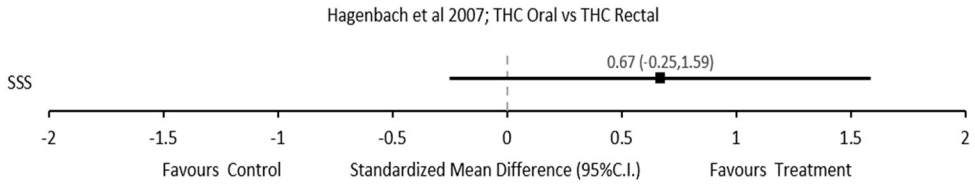
Ultramicronized palmitoylethanolamide (PEA/Normast)
is not effective in reducing pain post-SCI.

Preliminary results suggest that dronabinol
is not effective in reducing neuropathic pain post-SCI.

2.2 Spasticity

Table 2. Spasticity, Cannabinoids and SCI

Author Year Country Research Design Score Total Sample Size	Methods	Outcome
Nabilone		
Pooyania et al. 2010 Canada RCT Crossover PEDro=8 Level 1 N=11	**Population:** Mean age: 42.4 yr: Gender: males=11, females=0; Injury etiology: traumatic, non-traumatic SCI; Level of injury: tetraplegia=6, paraplegia=5; Time since injury: >1yr. **Intervention:** Individuals received either nabilone in tablet form or placebo during 4 wk. period (0.5-1.0 mg/day) with crossover design with 2 wk. wash-out period in between. **Outcome Measures:** Ashworth Scale (AS), Spasm Frequency Scale (SFS), Visual Analog Scale (VAS), Wartenberg Pendulum Test, Global Impression of Change.	1. A significant decrease in SFS, as measured by the AS, was observed for those on active treatment in the most involved muscle (mean difference=0.909±0.85; p=0.003), as well as for muscles overall (p=0.001). 2. There was no significant difference in other measures. 3. Side effects were mild and tolerable.
	Effect Sizes: Forest plot of standardized mean differences (SMD±95%C.I.) as calculated from pre- and post-intervention data. 	
Tetra-9-tetrahydrocannabinol (dronabinol)		
Hagenbach et al. 2007	**Population**: Age range: 29-66 yrs; Gender: males=11, females=2; Injury etiology: SCI=15; Level of	1. Phase 2 (RCT): main comparison (dronabinol versus placebo) was not analyzed due to potential

Switzerland Phase 1–Pre-post Level 4 Phase 2–RCT PEDro=6 Level 1 N=22 (RCT N=13)	injury: C4-T11; Level of severity: AIS: A, B, C, D. **Intervention:** Phase 1–Open label oral and rectal detra-9-tetrahydrocannabinol (dronabinol). Phase 2- Oral detra-9-tetrahydrocannabinol (dronabinol) versus placebo. **Outcome measures:** Spasticity Sum Score (SSS) (average of 2 x independent left/Right Modified Ashworth Scale (MAS) scores of 6 joints), Self-rating of spasticity and side effects.	confounds associated with large baseline group differences on SSS. 2. Phase 1 (pre-post dronabinol/rectal THC): mean SSS decreased significantly during active treatment compared to control on day one ($p<0.001/p<0.05$), day 8 ($p<0.001/P<0.05$) and day 43 ($p<0.05/p<0.05$) of treatment. 3. Phase 1 vs 2: (open label dronabinol versus placebo): 4. Mean SSS decreased significantly relative to placebo over days 1, 8 and 43 by a mean of 4.89 as compared to baseline ($p=0.001$). 5. Significant decrease in self-rated spasticity on day 1 ($p=0.033$) but not for days 8 or 43 ($p>0.05$). 6. No significant differences on mood or psychological testing, nor on FIM scores in intervention versus placebo groups. 7. Total of 9 dropouts during open-label phases were due to increased pain, anxiety, decreased compliance, decreased attention and mood.
	Effect Sizes: Forest plot of standardized mean differences (SMD±95%C.I.) as calculated from pre- and post-intervention data. 	
Wilsey et al. 2016 USA RCT Crossover PEDro=8 Level 1 N=42 (29 SCI)	**Population**: Mean age=46.4±13.6 yrs; gender: males=29, females=13; Level of injury: C=22, T=14, L=6. Intervention: crossover design with placebo, 2.9% and 6.7% THC vapour; 4 puffs at t=0 and 4 puffs at t=240 min. Treatment periods were 480 min. for each exposure with measurements every 60 min. **Outcome Measures**: Numeric Rating Scale of Spasticity (NRSS) for spasms, pain and muscle stiffness & Patient Global Impression of Change (PGIC)	1. 2.9% THC group: spasticity was significantly reduced at t = 420 min. ($p<0.0001$) and patients experienced pain relief at t = 420 ($p=0.0227$). No significant results at other measure points. 2. 6.7% THC group: no significant change in spasticity

Kogel et al. 1995 USA Pre-Post Level 4 N=5	**Population:** Age range: 28-55 yrs; Gender: males=5, females=0; Level of injury: tetraplegia; Time since injury range: 6 mos–9 yrs. **Intervention:** Open label design: Oral detra-9-tetrahydrocannabinol (dronabinol), with dose escalation: 2x5mg/day – 4x10 mg/day – 3x20mg/day) + current spasticity regimen. **Outcome Measures:** Pendulum Drop Test, Weschler Memory Scale (WMS), Profile of Moods Scales (POMS).	1. Spasticity was markedly improved in 2 of 5 subjects. 2. Results fluctuated in one participant, did not change in one participant, and worsened in another participant. 3. Psychological testing was unchanged (n = 4), with 2 improving on memory testing
Non-Specified Types		
Malec et al. 1982 USA Observational Level 5 N=43	**Population:** Age range: <20-60+ yrs; Gender: males=38, females=5; Injury etiology: 43; Time since injury range: 6 mo-5+ yr. **Intervention:** Survey to examine the perceived effects of cannabis on spasticity. **Outcome Measures:** Customized cross-sectional survey addressing demographic information (age range, sex, marital status, education, and range of time since injury), marijuana use, belief patterns associated with use, severity of spasticity associated with use/non-use, Spasticity Change Index, computed by subtracting level of spasticity in the drug-state from the non-drug-state.	1. SCI persons reported decreased spasticity with marijuana use; present use of marijuana correlated positively with past use. 2. The person's reference or peer group contributed significantly to current use. 53% reported using marijuana during last year with correlation to use prior to SCI ($r=0.78$, $p<0.001$, $n=43$; agrees with other studies). Also correlated with degree of use in present social reference group ($r=0.32$, $p<0.05$, $n=38$) and prior social reference group ($r=0.30$, $p<0.05$, $n=37$). Age was negatively correlated with current use ($r=-0.56$, $p<0.001$, $n=43$). 3. Reduction in spasticity via use was reported in 88% (21/24) while 12% reported no change. 4. No correlation between Spasticity Change Index and any variable (if significant correlation, then perhaps placebo effect). 5. Education moderately correlated with reported change in spasticity ($r=-0.65$, $p<0.001$, $n=23$): lower education associated with greater reported change in Spasticity Change Index. Marijuana use prevalence (53%, 23/43) among SCI surveyed and especially of SCI <30 yr (76%, 16/21).

Discussion

Hagenbach et al. (2007) performed a trial consisting of two open label phases; (I) dronabinol (oral THC) and (II) rectally delivered THC (followed by (III) double-blind, randomized, placebo control phase of oral dronabinol to evaluate efficacy and side effects for the treatment of SCI related spasticity. The main outcomes were the spasticity sum score (SSS) using the Modified Ashworth Scale as well as self-rating of spasticity. Due to numerous dropouts within the open label phases, the baseline SSS between groups were too large to perform the main analysis of phase III (dronabinol vs. placebo). In the open label phase, significant reductions in spasticity were seen in both oral and rectal THC groups. Analysis of dronabinol (phase I) versus placebo (phase III) was done instead: mean SSS decreased significantly on day 1 ($p=0.001$), day 8 ($p=0.001$) and day 43 ($p=0.05$). Self-rated spasticity decreased significantly on day 1 ($p=0.033$) but not day 8 or 43. There were no significant differences found with the remaining outcome measures. Due to the limitations in analysis, it remains unclear if placebo effects may have contributed to the positive findings in this study. We assign it a lower level of evidence (i.e., level 2) than would be expected of an RCT (i.e., PEDro≥6 = Level 1 RCT).

Pooyania et al. (2010) performed a double-blind, placebo-controlled, crossover trial of nabilone (0.5-1.0 mg/day) vs. placebo for 4 weeks for each treatment period with a 2-week washout period in between. They found a significant decrease in spasticity for those on active treatment ($p=0.003$) and overall muscles ($p=0.001$). There were no significant differences in other outcome measures. Contrary to Hagenbach et al. (2007), they reported only mild and tolerable side effects in this trial.

Wilsey et al. (2016) performed a crossover trial of placebo, 2.9% and 6.7% THC with a treatment time of 480 min. Participants took 4 puffs at t = 0 and 4 puffs at t = 240 min. They found a significant reduction of spasticity measured on a spasticity severity scale for 2.9% THC at t = 420 min. ($p<0.0001$) with significant spasticity relief ($p=0.0277$) but found no significant differences for the 6.7% THC group at any measurement points.

Kogel et al. (1995) performed a pre-post trial of dronabinol with dose escalation (2x5mg/day – 4x10 mg/day – 3x20mg/day) in five males with paraplegia. Two participants showed significant improvement in the pendulum test for spasticity, 1 showed fluctuating responses, 1 had no change and 1 had worsened.

Conclusion

There is level 1b evidence (from one RCT; Pooyania et al. 2010) that nabilone is effective in reducing spasticity in both the involved and overall muscles.

There is level 1b evidence (from one RCT; Wilsey et al. 2016) that 2.9% THC vapour is effective in reducing spasticity measured on a spasticity severity scale 420 min after 4 inhalations and 180 min after 4 additional inhalations.

There is level 2 evidence (from one compromised RCT; Hagenbach et al. 2007 and supported by one pre-post study; Kogel et al. 1995) to support the use of oral delta-9-tetrahydrocannabinol (dronabinol) in reducing both objective and subjective measures of spasticity.

Key Points

Nabilone in tablet form and 2.9 % THC vaporized have been shown to be effective in reducing spasticity, but additional research is needed.

Oral detra-9-tetrahydrocannabinol (dronabinol) may help to reduce spasticity but requires additional evidence from controlled studies.

3 Non-Spinal Cord Injury Evidence of Cannabis as Treatment

Meta-analyses show that cannabis seems to have a small positive effect on pain (Allan et al. 2018) and spasticity management (Allan et al. 2018; Whiting et al. 2015), as well as cancer-induced nausea and vomiting, but has no effects on cancer-related pain (Allan et al. 2018). For anxiety (NAS, 2017; Whiting et al. 2015), sleep quality, and sleep conditions (Whiting et al. 2015), there is not enough evidence to do a meta-analysis nor to adequately report on the efficacy of cannabis. Most studies included in meta-analyses on cannabis in the non-SCI literature are of low quality, mostly due to small group sizes and varying types of cannabinoids, modes of administration and dosage used (Whiting et al. 2015). This makes the scientific value of this evidence low. Some guideline recommendations show that cannabinoids produce analgesia in central neuropathic pain states. There are several studies where cannabis is used for management of HIV neuropathy, post trauma or post surgery, allodynia, as well as combinations of central and peripheral neuropathic pain (Moulin et al., 2014).

3.1 Pain

Mücke et al. (2018) conducted a meta-analysis that included 1,750 participants, of which 712 were people with Multiple Sclerosis (MS) and 1,038 were people with central or peripheral pain or with other aetiologies, including diabetic polyneuropathy, plexus neuropathy, or unknown/mixed aetiologies. Small positive effects were found for neuropathic pain reduction (Mücke et al. 2018) and inhaled cannabis resulted in short-term reductions in chronic neuropathic pain for 1 in every 5 to patients treated (Andreae et al. 2015). Allan et al. (2018) meta-analysis described a small positive effect on central pain and chronic pain reduction in a subgroup of 298 patients with MS from seven RCTs. A third meta-analysis on cancer-related pain showed no benefit of cannabis therapy when added to “care-as-usual” for individuals with advanced cancer (Boland et al. 2020).

3.2 Spasticity

The combined effects of studies predominantly done on multiple sclerosis (MS) patients found that cannabis improved self-reported spasticity in 50% of patients; compared to 35% of patients taking a placebo pill (Allan et al. 2018; Whiting et al. 2015).

3.3 Nausea and Vomiting

In a sample of patients on chemotherapy (N=1,215) or in palliative care (N=307), 47% of participants using cannabis, compared to 13% taking a placebo described control of nausea and vomiting (Allan et al. 2018). When we compare cannabis to medications frequently prescribed for nausea (neuroleptics) the effect is a little less convincing, but still substantial: 31% of cannabis patients were able to control nausea and vomiting versus 16% of patients for the other medications. However, patients on cannabis preferred cannabis over the other medications. Whiting et al. (2015) showed that the average number of patients who show complete resolution of nausea and vomiting response is greater in cannabinoids than placebo, but quality of the included studies was low due to small sample size, especially for the trial of glaucoma (N=6), Tourette syndrome (average N=18), sleep disorder (average N=27), and anxiety disorder (N=24) (Whiting et al. 2015).

3.4 Anxiety

A small study (N=24) showed some effect of cannabis on people with generalized anxiety disorder compared to placebo for a simulated public speaking trial (Bergamaschi et al. 2011). Additional trials show effects on non-specified anxiety symptoms in non-anxiety disorder patients, but effects were limited (NAS, 2017; Whiting et al. 2015). Anxiety symptom outcomes in people with chronic pain suggest a greater effect of cannabinoids than the placebo (Whiting et al. 2015).

3.5 Sleep

There are some positive effects of cannabis (containing both THC and CBD) on sleep problems like insomnia, sleep apnea and sleep restlessness (Whiting et al. 2015). It also seems to improve sleep quality and restfulness in patients without sleep issues, though this effect has only been measured short term (Whiting et al. 2015). The main issue with the studies on sleep, in addition to their small effects, is that they are short in duration; it is expected that tolerance and then dependence will develop. In individuals using larger amounts of cannabis for a longer time, a 'rebound' effect is found on sleep; causing insomnia after ceasing cannabis use (Babson et al. 2017). The effects on sleep of products containing only CBD have not been sufficiently studied yet, but laboratory studies suggest that CBD has a stimulating effect in low doses and a sedating effect in high doses; low dose CBD may increase total sleep time and decrease frequency of awakenings during the night (Carlini & Cunha 1981).

The usefulness of these findings is limited by sample size, variations across studies in cannabis products, cannabis production methods, properties of cannabinoid types and ratios, dosage

regimens, and methods of administration. For example, comparing a study of 7% vaporized synthetic THC with a study that used a plant-derived 1:1 THC to CBD ratio cannabis edible is difficult and leaves us guessing about the ideal or preferred cannabinoid medication. Lastly, it is important to note that the effects measured in these studies were small and the clinical relevance falls within a grey area; therefore, it will be up to the clinician to determine what is clinically relevant versus what has been established experimentally.

4 Risks and Side Effects of Cannabis Use

Side effects common in the SCI population using cannabis include dry mouth, fatigue, and hunger (Nabata et al. 2020). Most short-term side effects are mild to moderate and dose-dependent (NAS, 2017). Naïve users of cannabis may experience acute overdose symptoms including feelings of anxiety and panic, combined with nausea, vomiting, and possibly fainting as well as symptoms of misperception and distortion of time and space (Hagenbach et al., 2007; Wilsey et al, 2008; Office of Medical Cannabis of the Netherlands, 2019). Studies show that autonomic, cardiovascular, and respiratory side effects are not common in SCI patients using cannabis, but more research is needed (Nabata et al. 2020; Hagenbach et al., 2007; NAS, 2017). Cannabis use may lead to depressive and anxious symptoms, though these are not commonly reported by SCI patients in studies. Long term use of cannabis is associated with tolerance, dependence, and withdrawal symptoms when long-term use is ceased (Hall & Degenhardt (H&D), 2009; NAS 2017). Some individuals develop cannabis dependence syndrome; life-time risk is 9% for cannabis users in general. Long term use of cannabis is associated with chronic psychotic illness, usually before the age of 26, though causality is unclear (H&D, 2009; Arsenault et al. 2002). There is a need for more high-quality research studies with a rigorous design, that are longer-term, and follow a double-blinded, randomized controlled trial design.

Risks and side effects associated with therapeutic and recreational use of cannabis in the general population has been studied more than in those with spinal cord injury. Many short-term side effects were dose-dependent and were reported as mild to moderately severe (NAS, 2017). These included red, dry eyes that feel heavy, altered skin sensations of cold/heat and increased hunger (H&D, 2009). A few studies report on side effects as secondary outcomes in SCI studies and showed that dry mouth, fatigue and hunger are the most common side effects, and they tend to be experienced as mild. Moderate side effects reported included constipation, fatigue and abdominal discomfort, no severe side effects were reported (Nabata et al. 2020). In the general population the most common short-term physical side effects include dry mouth, muscle weakness, headache, light-headedness, dizziness, irritation of airways and tachycardia (NAS, 2017; H&D, 2009). There is a weak association between cannabis use and psychosis, and other studies show no increased psychosis incidence (H&D 2009). However, other studies show that a baseline history of cannabis use increases the risk of a follow-up psychosis outcome for patients with no previous psychosis outcomes. Long-term effects of cannabis on risk of psychosis outcome may be due to dysregulation of endogenous cannabinoid systems (van Os et al., 2002). The risks associated with smoking cannabis are like smoking tobacco (Health Canada, 2018). All routes of administration, such as orally, rectally, and parenterally, are free of the risk of chronic inflammatory disease and upper respiratory cancer.

4.1 Autonomic Functions

Few autonomic side effects with cannabis use have been reported for people with SCI (Nabata et al. 2020) but given the typical prevalence of autonomic dysfunction in spinal cord injury, these functions should be closely monitored. Wade et al. (2003) showed no effect on incontinence frequency or severity, bladder urgency, or nocturia per night. No reported impact on ECG in two studies (Hagenbach et al. 2007; Wilsey et al. 2016). Following a 6-week intervention of dronabinol, blood pressure significantly decreased in the intervention group, in comparison to increased blood pressure among people in the placebo group (Hagenbach et al. 2007). Decreased blood pressure may be a risk for a side event (e.g., fall), for those with postural hypotension. Prolonged use of cannabis administered by inhalation has been associated with increased risk of chronic obstructive pulmonary disease (COPD), chronic bronchitis, and recurring respiratory infections (NAS, 2017). Prolonged cannabis use has also been associated with a slightly increased chance of triggering a myocardial infarction in high risk individuals (NAS, 2017), as well as with increased mortality rates after myocardial infarction in frequent cannabis users in comparison to myocardial infarction patients who were not frequent users of cannabis (H&D, 2009). A recently published case report identifies that cannabis use improved blood pressure stability by reducing intensity and frequency to the visceral stimuli (Nightingale et al., 2020).

4.2 Cognition

Cannabis and THC produce dose-related impairments in reaction time, information processing, perceptual–motor coordination, motor performance, attention, and tracking behaviour (NAS, 2017; H&D 2009). Moreover, cannabis lingers in the body long after use, particularly in fatty tissues like the brain, meaning task performance may be impaired long after the psychoactive effects wear off. Experimental studies with SCI show mixed results on cognition with side effects like a decrease in objective concentration, memory, learning and psychomotor speed reported by participants taking THC rich products (Wilsey et al. 2008; Wade et al. 2003), whereas other studies show no side effects on cognition in people with SCI when using THC rich products or THC/CBD mixed products (Kogel et al. 1995; Hagenbach et al. 2007; Wade et al. 2003). It is recommended to avoid operating heavy machinery or performing dangerous activities for 3 hours after inhaling cannabis, 6 hours after oral ingestion of cannabis, and 8 hours if a “high” is experienced (Kahan et al. 2014). Driving laws in Canada state that driving after using cannabis is a punishable offence. Cannabis tests are positive when a blood serum value of 2 ng/ml or more two hours after driving is registered (Brubacher et al. 2019; by comparison, one inhalation of 100 mg of standardized 9.4% THC cannabis will raise serum levels to 45 ng/ml) and combined with the unpredictable half-life time of THC and its metabolites, it is hard to estimate when driving is safe and legal after using cannabinoids. It is therefore advisable to never mix cannabis use and driving. Examples of high-risk activities with regards to SCI may include performing transfers, operating heavy machinery, and participating in physical therapy sessions. Cannabis-induced cognitive impairment has been shown to be reversible within 2-3 months when cannabis use is stopped (NAS, 2017).

4.3 Mental Health and Wellness

In the non-SCI population, long term use has been associated with physical dependence and withdrawal; this causes a range of symptoms, most notably anxiety, restlessness, irritability, insomnia, and nausea. Cannabis use is also associated with an increased chance of mood and anxiety disorders, as well as decreased motivation. Two experimental studies in SCI showed no effects of cannabis on mood and emotion (Hagenbach et al. 2007; Wilsey et al, 2008) and one study showed a decrease of vigor and an increase in at least one dysphoric mood state (anger, tension) in participants taking dronabinol (Kogel et al. 1995). Acute intoxication by taking a high dose of THC in a short amount of time can cause feelings of anxiety and panic, combined with nausea, vomiting and possibly fainting as well as symptoms of misperception and distortion of time and space; briefly altering how one perceives and experiences the world (Office of Medical Cannabis of the Netherlands, 2019). These negative effects are most often reported by new users (naïve cannabis users) and are considered an acute overdose in relative terms; physically overdosing on cannabis requires immense amounts being ingested in a short period of time (NAS, 2017).

Long term cannabis use has been associated with chronic psychotic disorders, most notably schizophrenia. It is still unclear if cannabis use *causes* schizophrenia, *triggers* schizophrenia in at-risk individuals, or if individuals who *already have* schizophrenia use cannabis to self-medicate (NAS, 2017). An emerging concern is the potentially greater side effects that cannabis use may have on adolescents and young adults. Cannabis use early in adolescence may alter brain development and could be related to the development of psychotic disorders as adults (H&D, 2009; NAS, 2017). Long-term use can also lead to cannabis dependence syndrome, which consists of a combination of tolerance to effects, impaired control over use, psychological and cognitive side effects and a failure to cease usage despite its harmful effects (H&D, 2009; NAS 2017). Lifetime risk for cannabis users developing cannabis dependence syndrome is 9% (H&D, 2009). This risk increases when age of initiation is earlier, with dose, and with frequency of use. (NAS, 2017).

Illegal synthetic cannabinoids are made to imitate the psychoactive effects of THC but are made of different substances; this makes their effects on the body highly unpredictable (National Center for Environmental Health, 2018). Illegal synthetic cannabinoids compounds like “K2” and “Spice” are often combined with plant-based cannabis products or mixed with other dangerous and often addictive substances and have been responsible for serious side-effects and overdoses (Canadian Centre on Substance Abuse, 2014). Production, distribution, and use associated with non-prescription synthetic cannabinoids are illegal in Canada (Health Canada, 2013). Besides their varying concentrations, their capacity to bind with the cannabinoid receptors of the body is usually much stronger, increasing risk of overdose.

5 Conclusion/Future Directions

Cannabis in SCI is a developing field of research but few methodologically robust studies with large groups have been conducted. Studies done to date show moderate evidence that cannabis may help against pain in SCI and conflicting evidence that it helps with spasticity. Though meta-

analyses have been conducted, the findings must be interpreted cautiously, as combining studies of lower quality to do not strengthen the quality of the research (Allan et al. 2018). There are many side effects that can arise when taking cannabis, the most common of which are dry mouth, fatigue, and hunger; most side effects are considered mild to moderate, though some studies show substantial dropouts due to side effects. Further studies are needed on cannabis in SCI to have more definitive evidence about the potential treatment effects for pain and spasticity, as well as other symptoms. As more patients are enrolled in higher quality trials with larger groups, we would hope to gain more information on the effectiveness and the side effects on cannabis in SCI. Clinicians and health care professionals would particularly benefit from clinical trials that clarify what dosage and method of administration of cannabis products are beneficial for particular conditions. Lastly, studies that are longer in duration are necessary to study benefits and side effects of cannabis over time to more clearly understand its true potential.

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7 Abbreviations

AIS	ASIA Impairment Scale
AS	Ashworth Scale
ASIA	American Spinal Injury Association
AMSTAR	A MeaSurement Tool to Assess systematic Reviews
BPI	Brief Pain Inventory
CBD	Cannabidiol
CDC	Centre for Disease Control
CGI	Clinician Global Impression
CI	Confidence Interval

CINAHL	Cumulative Index to Nursing and Allied Health Literature
COPD	Chronic Obstructive Pulmonary Disease
FDA	Food and Drug Administration
MA	Meta-analysis
MAS	Modified Ashworth Scale
NAS	National Academy of the Sciences
NIH	National Institute of Health
NRS	Numeric Rating Scale
n.d.	Not dated
PEA	Palmitoylethanolamide
PEDro	Physiotherapy Evidence Database
PGIC	Patient Global Impression of Change
POMS	Profile of Moods Scales
PRISMA	Preferred Reviews and Meta-Analysis
SCI	Spinal Cord Injury
SFS	Spasm Frequency Scale
SGI	Subject Global Impression
SMD	Statistical Mean Difference
SR	Systematic Review
SSS	Statistical Sum Score
THC	Delta-9-tetrahydrocannabinol
VAS	Visual Analog Scale
WMS	Wechsler Memory Scale