Table 8: Summary of Recommendations in Included Guidelines

Evidence and Recommendations	Strength of Evidence and Recommendations
Systematic Review of Guidelines	
Deng,[8] 2016, China	
Evidence: It was reported that evidence-based approach was used, but details were not presented **Recommendation:** Three guidelines recommended the use of cannabinoids as fourth line analgesics for the management of neuropathic pain.	**Strength of Evidence:** Not reported **Strength of Recommendation:** Not reported
Guidelines	
Allan, [15] 2018, Canada	
<u>Headache</u> **Evidence:** **I**nsufficient evidence (1 flawed cross-over RCT) on benefit, and known harms **Recommendation:** "We recommend against use of medical cannabinoids for headache owing to lack of evidence and known harms (strong recommendation)" (*p.112*) **<u>Pain due to rheumatologic conditions</u>** (including fibromyalgia, osteoarthritis, rheumatoid arthritis, and back pain) **Evidence:** Insufficient evidence for benefit (reported in 3 systematic reviews) and high risk of harms **Recommendation**: "We recommend against use of medical cannabinoids for pain associated with rheumatologic conditions (including osteoarthritis and back pain) owing to lack of evidence and known harms (strong recommendation)" (*p.112*) **<u>Neuropathic pain:</u>** **Evidence:** One meta-analysis showed a greater number of patients achieved >30% pain reduction with cannabinoids. However sensitivity analysis using RCTs of large size or longer duration found no effect. Harms resulting from cannabinoids were consistent and common among the various conditions evaluated. One overview reported that the risk of adverse events and withdrawals were numerically higher with cannabinoids compared with placebo (adverse events: 80% versus 60%; withdrawals: 11% versus 3%). **Recommendations:** "We recommend against medical cannabinoids as first- or second-line therapy in neuropathic pain owing to limited benefits and high risk of harms (strong recommendation) -Clinicians could consider medical cannabinoids for refractory neuropathic pain, with the following considerations (weak recommendation): - a discussion has taken place with patients regarding the benefits and risks of medical cannabinoids for pain - patients have had a reasonable therapeutic trial* of ≥ 3 prescribed analgesics† and have persistent problematic pain despite optimized analgesic therapy	**<u>Headache</u>** **Strength of Evidence:** Not reported **Strength of Recommendation:** Strongly against **<u>Pain due to rheumatologic conditions</u>** **Strength of Evidence:** Not reported **Strength of Recommendation:** Strongly against **<u>Neuropathic pain:</u>** **Strength of Evidence:** Not reported **Strength of Recommendation:** Strongly against (with respect to cannabinoid use as first- or second line therapy); Weak (with respect to use of cannabinoids for refractory neuropathic pain)

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- medical cannabinoids are adjuncts to other prescribed analgesics" (*p112*) *Note:* "*Reasonable therapeutic trial is defined as 6 weeks of therapy with an appropriate dose, dose titration, and monitoring (eg, function, quality of life). †Other prescribed therapies for neuropathic pain management include, but are not limited to (in no particular order), tricyclic antidepressants (e.g.,, amitriptyline, nortriptyline), gabapentinoids (gabapentin, pregabalin), or selective norepinephrine reuptake inhibitor antidepressants (duloxetine, venlafaxine). The committee believed that ≥ 3 medications should be trialed before considering cannabinoids or opioids." (*p.112*)	
Hauser,[7] 2018, Germany	
Chronic neuropathic pain **Evidence:** One overview found that findings on efficacy of cannabinoids compared to placebo were inconsistent. One systematic review reported that inhaled cannabis appeared to provide short-term relief. No data on intermediate term were available A second systematic review reported that the between group risk difference with respect to >30% pain relief was not statistically significant. A third systematic review concluded that for short-term or intermediate term cannabis-based medicines may be considered in selective patients with chronic neuropathic pain, after first- and second line treatments have failed. A fourth systematic review concluded that there was no high-quality evidence suggesting the use cannabis-based medicines was of value. In addition, potential benefits might be outweighed by the potential harms associated with cannabis-based medicines **Recommendations:** "Cannabis-based medicines can be considered as third-line therapy for chronic neuropathic pain." (p.1553) **Chronic non-neuropathic non-cancer pain** **Evidence:** One systematic review concluded that there was insufficient evidence to support cannabis-based treatment for patients with chronic non-neuropathic non-cancer pain **Recommendation:** "In exceptional cases, cannabis-based medicines can be considered as an individual therapeutic trial, if all established treatments have failed and after careful analyses and multidisciplinary assessment." (p.1554)	**Strength of Evidence: Not reported** **Strength of Recommendation:** Not reported **Strength of Evidence: Not reported** **Strength of Recommendation:** Not reported
Australian Government,[19] 2017, Australia	
<u>Overall management of CNCP</u> **Evidence:** Not reported **Recommendations:** "A comprehensive sociopsychobiomedical assessment of the patient with CNCP is appropriate; The use of medications, including medicinal cannabis, is not the core component of therapy for CNCP; Patient education is a critical component of therapy for CNCP, particularly with respect to	**<u>Overall management of CNCP</u>** **Strength of Evidence:** Not reported **Strength of Recommendation:** Not reported

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expectations of drug therapy; and There is a need for larger trials of sufficient quality, size and duration to examine the safety and efficacy of medicinal cannabis use in CNCP." (*p3*) **Cannabinoids as second-line therapy for CNCP** **Evidence:** Evidence was derived using 102 studies (4 studies reported on cannabis as first-line therapy; 81 studies reported on cannabis as second-line therapy in addition to existing medication regimens; and 17 studies did not report the place of cannabis in the therapeutic hierarchy) **Recommendation:** "Most evidence on medicinal cannabis use in CNCP is derived from studies where cannabinoids were adjuvant interventions. Cannabinoids should not replace current approved first-line treatments for pain and there is significant potential for drug interactions which needs further study." (p14) **Tolerability of cannabinoids** **Evidence:** Evidence for the various types of cannabinoids was derived from several studies (number of studies varied between 1 and 10 depending on the type of cannabinoid) **Recommendation:** "Adverse effects of long-term medicinal cannabis use is poorly understood. Long term studies are required to explore this issue." (*p.19*) **Patient's response to cannabis treatment** **Evidence:** Duration of treatment in most RCTs and observational studies was less than 12 weeks. In three observational studies the duration of treatment was 12 months or longer. **Recommendation:** "In the absence of strong evidence for dosing and specific preparations of cannabis or cannabinoids in the treatment of CNCP, it is recommended that any treating physician who elects to initiate cannabinoid therapy should assess response to treatment, effectiveness and adverse effects after 1 month. This is best achieved as part of a research project or clinical audit." (*p.20*)	**Cannabinoids as second-line therapy for CNCP** **Strength of Evidence:** Not reported **Strength of Recommendation:** Not reported **Tolerability of cannabinoids** **Strength of Evidence:** Very low to moderate **Strength of Recommendation:** Not reported **Patient's response to cannabis treatment** **Strength of Evidence:** Not reported **Strength of Recommendation:** Not reported
CFPC,[18] 2014, Canada	
Evidence: For chronic neuropathic pain, the evidence was obtained from five controlled trials of small size and short duration (1 to 15 days). No information was available on functional status, quality of life and other important outcomes The safety and effectiveness of dried cannabis has not been studied for conditions such as fibromyalgia and back pain. **Recommendation 1:** "There is no research evidence to support the authorization of dried cannabis as a treatment for pain conditions commonly seen in primary care, such as fibromyalgia or low back pain (Level III). Authorizations for dried cannabis should only be considered for patients with neuropathic pain that has failed to respond to standard treatments (Level I)." (*p.3*)	**Strength of Evidence: Not reported** **Strength of Recommendation:** Level III or Leve I as indicated in the adjacent column.

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Evidence: Before considering treatment with cannabinoids, established effective pharmacological and non-pharmacological treatments need to be tried. **Recommendation 2:** "If considering authorizing dried cannabis for treatment of neuropathic pain, the physician should first consider a) adequate trials of other pharmacologic and nonpharmacologic therapies and b) an adequate trial of pharmaceutical cannabinoids (Level I). (*p.3*) **Other recommendations** not specifically for chronic pain are listed below but not discussed further. **Recommendation:** "Dried cannabis is not appropriate for patients who: a) Are under the age of 25 (Level II) b) Have a personal history or strong family history of psychosis (Level II) c) Have a current or past cannabis use disorder (Level III) d) Have an active substance use disorder (Level III) e) Have cardiovascular disease (angina, peripheral vascular disease, cerebrovascular disease, arrhythmias) (Level III) f) Have respiratory disease (Level III) or g) Are pregnant, planning to become pregnant, or breastfeeding (Level II)" (*p.3*) **Recommendation:** "Dried cannabis should be authorized *with caution* in those patients who: a) Have a concurrent active mood or anxiety disorder (Level II) b) Smoke tobacco (Level II) c) Have risk factors for cardiovascular disease (Level III) or d) Are heavy users of alcohol or taking high doses of opioids or benzodiazepines or other sedating medications prescribed or available over the counter (Level III)" (*p.3*) **Recommendation:** "Physicians should follow the regulations of their provincial medical regulators when authorizing dried cannabis (Level III). (*p4*) Recommendation: "Physicians should assess and monitor all patients on cannabis therapy for potential misuse or abuse (Level III)." (*p4*) Recommendation: "Before signing a medical document authorizing dried cannabis for pain, the physician should do all of the following: a) Conduct a pain assessment (Level II) b) Assess the patient for anxiety and mood disorders (Level II) c) Screen and assess the patient for substance use disorders (Level II)" (*p4*) **Recommendation:** The physician should regularly monitor the patient's response to treatment with dried cannabis, considering the patient's function and quality of life in addition to pain relief (Level III). The physician should discontinue authorization if the therapy is not clearly effective or is causing the patient harm. (Level III)." (*p.4*)	

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Recommendation: "Patients taking dried cannabis should be advised not to drive for at least: a) Four hours after inhalation (Level II) b) Six hours after oral ingestion (Level II) c) Eight hours after inhalation or oral ingestion if the patient experiences euphoria (Level II)" (*p4*) **Recommendation:** "When authorizing dried cannabis therapy for a patient, the physician should advise the patient of harm reduction strategies (Level III)."(*p.4*) **Recommendation:** "The physician should manage disagreements with patients about decisions around authorization, dosing, or other issues with unambiguous, evidence-based statements (Level III). "(*p.4*) **Recommendation:** "The physician who is authorizing cannabis for a particular clinical indication must be primarily responsible for managing the care for that condition and following up with the patient regularly (Level III). Physicians seeking a second opinion on the potential clinical use of cannabis for their patient should only refer to facilities that meet standards for quality of care typically applied to specialized pain clinics (Level III). In both instances, it is essential that the authorizing physician, if not the patient's most responsible health care provider, communicate regularly with the family physician providing ongoing comprehensive care for the patient (Level III)." (*p.4*) **Recommendation:** "Given the weak evidence for benefit and the known risks of using cannabis, the only sensible advice for physicians involved with authorizing dried cannabis is the maxim "Start low, and go slow" (Level III)." (*p.5*) **Recommendation:** Although it is not required by the MMPR, physicians should specify the percentage of THC on the medical document for all authorizations for dried cannabis, just as they would specify dosing when prescribing any other analgesic (Level III). (*p.5*)	
Moulin (Canadian Pain Society),[16] 2014, Canada	
Evidence: Three trials found positive effects with cannabinoids in terms of pain management. In addition, one systematic review including seven trials found positive effects in six trials and negative effect in one trial with cannabinoids in terms of pain management. **Recommendation:** "One class of medication is recommended for third-line treatment in the management of NeP – cannabinoids." (*p.330*) It was also mentioned that use of cannabinoids is recommended but judicious prescribing practices are required.	**Strength of Evidence:** Not reported **Strength of Recommendation:** Not reported
Yadav (American Academy of Neurology),[17] 2014, US	

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Evidence and Recommendations	Strength of Evidence and Recommendations
Evidence 1 Evidence obtained from studies: two Class I, one Class II, and one Class III. **Recommendation 1:** "Clinicians might offer OCE to patients with MS to reduce patient-reported symptoms of spasticity and pain (excluding central neuropathic pain) (Level A)" (*p.1087*)	**Evidence 1:** Class I, II and III. **Recommendation 1:** Level A
Evidence 2 Evidence obtained from studies: one Class I and one Class II . **Recommendation 2:** "Clinicians might offer THC to patients with MS to reduce patient-reported symptoms of spasticity and pain (excluding central neuropathic pain) (Level B)." (*p.1087*)	**Evidence 2:** Class I and II. **Recommendation 2:** Level B
Evidence 3: Evidence obtained from one Class I study each, for the outcomes mentioned in the associated recommendation below. **Recommendation 3:** "Clinicians might offer Sativex oromucosal cannabinoid spray (nabiximols), where available, to reduce symptoms of spasticity, pain, or urinary frequency, although it is probably ineffective for improving objective spasticity measures or number of urinary incontinence episodes (Level B)." (*p.1087*)	**Evidence 3:** Class I. **Recommendation 3:** Level B
Evidence 4: Insufficient evidence **Recommendation 4:** "Data are inadequate to support or refute use of the following in MS (Level U): […] Smoked cannabis for spasticity, pain, balance/posture, and cognition" (*p.1088*)	**Evidence 4:** Insufficient. **Recommendation 4:** Level U

CNCP = chronic non-cancer pain; MMPR = Marihuana for Medical Purposes Regulations; MS = multiple sclerosis; NeP = neuropathic pain; OCE = oral cannabis extract; RCT = randomized controlled trial; THC = delta-9-tetrahydrocannabinoid.