Appendix

Minimal important difference

For the determination of minimal important differences in clinical trials two types of methods are available; anchor-based methods and distributional-based methods [1].

Anchor-based methods

Anchor-based methods relate the change in on a person reported outcome score, (e.g. a score on the visual analog scale (VAS)) to a subjective global assessment rating (e.g. scores from the Clinical Global Impressions-Improvement (CGI-I)) which is used as an 'anchor' [1]. Ideally, there needs to be an established association between the person reported outcome score and the 'anchor' to make any meaningful inference about a minimal important difference [2].

There are two subtypes of anchor-based methods, i.e., the '*within-patient score'* and the *'between-patients score'* [1].

- Within-patient score defines minimal important difference as the average minimal change in a given person's reported outcome score that leads to a clinically observable change in the subjective global assessment rating (the latter is used as an anchor) [1]. For example, to ascertain the minimal important difference regarding depression management, Moncrieff et. al describes the linking of within-patient scores (change from baseline) scores on the Hamilton Depression Rating Scale (the most commonly used depression rating scale) to scores on the Clinical Global Impressions-Improvement (CGI-I) scale, a scale which rates improvement on a scale of 1 (very much improved from baseline) through 4 (no change from baseline) to 7 (very much worse from baseline) [3]. Moncrieff et. al conclude that seven points on the Hamilton Depression Rating Scale correspond to a minimal important difference when using within-patient scores [3].
- The between-patients score method, also known as 'the group difference' method, compare the reported outcome scores between a group of people with no clinically observable change (based on a subjective global assessment rating (used as an anchor)) to a group of people with clinically observable change (based on a subjective global assessment rating (used as an anchor)). The minimal important difference is then estimated as the mean difference between these two groups [4]. For example, Musoro et. al defines the minimal important difference (MID) as the group difference in terms of quality of life assessed by HRQOL scores [5]. Participants were assigned to distinct subgroups reflecting various levels of change (e.g. no change, small positive changes, large positive changes, small negative changes or large negative changes). The group difference was identified by the

comparison of the average of the HRQOL scores of the group of participants with at 'small change' to the HRQOL scores of the group of participants with 'no change' [5].

There are also other anchor-based methods (e.g. the sensitivity- and specificity-based method and the social comparison method) [1]. The sensitivity- and specificity-based method aims to identify the minimal important difference that allows for the best discrimination between groups of patients (i.e., the score that produces the greatest sensitivity and specificity) [1]. For example, an outcome measure (e.g. NRS score) is considered a 'diagnostic test' and the anchor (e.g. Global Perceived Effect) is used as gold standard and hence standard methods may be used to estimate sensitivity and specificity. Sensitivity is the proportion of patients who report an improvement on the external criterion (anchor) and whose person reported outcome scores are above the threshold minimal important difference value [1]. Specificity is the proportion of patients who do not report an improvement on the external criterion (anchor) and whose person reported outcome scores are below the threshold minimal important difference value [1]. Receiver operating characteristic (ROC) curves are then used to identify the person reported outcome score with the greatest sensitivity and specificity [6-8].

The distributional-based methods

Distribution-based methods are based on the statistical characteristics of the obtained sample [9]. Crosby et. al [9] have identified two general types of distribution-based methods for estimations of minimal important differences:

- The first type of distribution-based method evaluate change in relation to sample variation [9]. Different types of variation can be used: effect size, standardised response mean, and responsiveness statistic [9]. The effect size represents individual change in relation to the number of pre-test standard deviations (SDs) [9]. Cohen et. al has suggested benchmarks to better interpret the effect sizes: .20 for ''small'' effects, .50 for ''moderate'' effects, and .80 for ''large'' effects [10]. Whereas the effect size is the ratio of individual change to the baseline standard deviation of the sample, standardised response mean is the ratio of individual change to the standard deviation of that change [11]. A large standardised response mean indicates that the change is large in comparison to the background variability in the measurements [9]. Guyatt et. al has proposed a responsiveness statistic as a variation of standardised response mean; calculated by dividing the difference between pre-test and post-test by the standard deviation of change observed for a group of stable participants [12].

- The second type distribution-based method is based on the measurement precision of the instrument [9]. This method include the standard error of the mean (SEM) and evaluate the change in relation to variation of the instrument as opposed to variation in the sample [9]. Standard error of the mean (SEM) is a measure of the precision of a test instrument and considered an attribute of the measure and not a characteristic of the sample per se [13]. The standard error of the mean (SEM) for a given measure is likely to vary across samples depending upon the method used to estimate reliability and the presence of extreme scores [9]. Different thresholds for a minimal important difference have been suggested, i.e., values of 1 SEM [14], 1.96 SEM [15], and 2.77 SEM [13, 15].

In conclusion, different methods for estimating minimal important differences exist, but no single method has been shown to be the optimal method. The question of whether to use anchor-based or distribution-based methods for determining clinically meaningful change has received considerable attention and debate [9]. Dworkin et. al defined the clinical importance of patient improvement as the clinically important changes in individuals that can be identified using either within-patient anchor-based method or distributional-based method [16, 17], while the clinical importance of group differences could be the clinical difference between a treatment group and a placebo group or between two different treatment groups [18]. Dworkin et. al claim that the clinical important difference identified in individuals cannot be directly extrapolated to the evaluation of group differences [17, 19-22]. The U.S. Food and Drug Administration also states in their web site “When defining meaningful change on an individual patient basis, that definition is generally larger than the minimum important difference for application to group mean comparisons” [22].

While it is claimed that the within-patient differences are larger than the between-group difference [22], based on the studies included in our review we are not able to find a significant difference between the minimal important difference estimated by the two different methods.

Previously conducted reviews on this subject

- Lynch & Campbell and Boychuk et. al both concluded that cannabinoids are a modestly effective and a safe treatment option for neuropathic pain [23, 24]. Lynch & Campbell and Boychuk et. al did not publish a protocol on beforehand [23, 24].
- Meng et. al concluded that there is moderate quality evidence to suggest that nabiximols (phytocannabinoid mixture) is effective in reducing neuropathic pain [25].

- Mücke et. al concluded that there is no high-quality evidence for the efficacy of any cannabis-based medicine in any condition with chronic neuropathic pain [26]. Mücke et. al further concluded that some adverse events may limit the clinical usefulness of cannabis-based medicines [26].
- Deshpande et. al concluded that current evidence suggests that very low-dose medical marijuana (< 34 mg/d) is associated with an improvement in refractory neuropathic pain of moderate severity in adults using concurrent analgesics. Deshpande et. al did not publish a protocol on beforehand [27].
- Martín-Sánchez et. al concluded that treatment of chronic pain based on cannabinoid compounds would entail more risk of adverse events than benefit [28]. Martín-Sánchez et. al included trials randomising participants with either neuropathic pain, cancer pain, fibromyalgia related pain and nociceptive pain [28]. Martín-Sánchez et. al did not publish a protocol on beforehand [28].
- Aviram et. al concluded that cannabinoid-based medicines were not effective for postoperative pain, however further investigation is advised [29]. Aviram et. al also concluded that evidence suggests a moderate to good treatment effect on neuropathic pain [29]. Furthermore, neuropathic pain patients should be advised that the inhalation of cannabinoids showed relatively better pain reduction effects than other routes of administration [29]. Aviram et. al stated that the total number of adverse events that were accumulated in the meta-analysis indicated that cannabinoid-based medicines should be used with caution [29]. Aviram et. al did not publish a protocol on beforehand [29].
- Campbell et. al concluded that levonantradol (synthetic cannabinoid analogue) was superior to placebo on postoperative pain but no more effective than codeine [30]. Campbell et. al also stated that there are suggestions of efficacy in spasticity and in neuropathic pain and that increasing the cannabinoid dose to increase the analgesia will increase adverse effects [30]. Campbell et. al did not publish a protocol on beforehand [30].
- Stevens et. al concluded that cannabinoids have no role in the management of acute pain, but cannabinoids were found to be well-tolerated, with most reported adverse effects only mild to moderate in severity [31].
- Walitt et. al concluded that no convincing, unbiased evidence suggests that nabilone (synthetic cannabinoid analog) is of value in treating people with fibromyalgia [32]. The tolerability of nabilone was low and adverse events (particularly somnolence, dizziness, vertigo) may limit its clinical usefulness [32].

TABEL 1

First author	Title	Year of publication	Design	Type of cannabinoid	Types of participants	Information sources	No. of trials	No. of participants	Published protocol	Outcomes	Assessment of adverse events	Assessment of risk of bias	Accounts for random error	Use of the GRADE	Conclusion
Lynch & Campbell [23]	Cannabinoids for treatment of chronic non-cancer pain; a systematic review of rando	2011	Systematic Review	**Phytocannabinoids;** Smoked cannabis, oromucosal extracts of cannabis-based medicine, and **synthetic cannabinoids**; nabilone, dronabin	Neuropathic pain, fibromyalgia, rheumatoid arthritis, and mixed chronic pain.	PubMed, EMBASE, CINAHL (EBSCO), PsycInfo (EBSCO), The Cochrane Library, ISI Web of Science, ABI Inform (Proquest), Dissertation Abstracts (Proquest), Academic Search Premie	18 trials comparing the intervention with placebo	766	No	The primary outcome was pain in subjects with chronic non-cancer pain. The secondary outcomes were sleep, function, and quality of life.	Yes	Yes, except for reporting bias, publication bias and for-profit bias	No	No	Overall there is evidence that cannabinoids are safe and modestly effective in neuropathic pain with preliminary evidence of efficacy in

	mized trials			ol and a novel THC analogue.		r (EBSCO), ClinicalTrials.gov, TrialsCentral.org, individual pharmaceutical company trials sites for Eli Lilly and GlaxoSmithKline, OAIster (OCLC) and Google Scholar.									fibromyalgia and rheumatoid arthritis. Did not pool data for meta-analysis but data was described qualitatively.
Meng et.al [25]	Selective Cannabinoids for Chronic Ne	2017	Systematic Review and M	Dronabinol, nabilone and nabiximols	Neuropathic pain	Medline, Embase, Cochrane Library, PROSPERO, clinicaltrials.gov, and Google	11 (10 trials comparing the int	1219	No	The primary outcome was intensity of pain recorded after a minim	Yes	Yes	Bonferroni adjustment for multiple testing was not	Yes	Selective cannabinoids provide a small analgesic benefit in patie

	uropathic Pain: A Systematic Review and Meta-analysis		eta-analysis			Scholar. Pain societies (American Society of Anesthesiologists, European Society of Anaesthesiology, International Association for the Study of Pain, American Society of Regional Anesthesia and Pain Medicine, European Society of Regional	ervention with placebo)			um of 2 weeks following initiation of selective cannabinoid and placebo/comparator administration, expressed on an NRS (0—no pain to 10—worst possible pain). Secondary outcomes were presence or absence of analgesia defined as reduction in pain scores			performed as per recommendations in the Cochrane Handbook.		nts with chronic neuropathic pain.

						Anesthesia and Pain Therapy, and World Institute of Pain) in the last 2 years were also searched.				(NRS/VAS) by ≥30% at 2 weeks or more after initiation of intervention, quality of life (QoL), physical function, psychological function, sleep, overall patient satisfaction, and the incidence of adverse effects of selective cannabinoids.					
Martín-Sá	Systematic Re	2009	Meta-anal	**Phytocannabinoids** and	Chronic pain	Medline/Pubmed, Embase, and	18	?	No	The primary outcome	Yes	Yes, except	No	No	Currently available evide

nchez et. al [28]	view and Meta-analysis of Cannabis Treatment for Chronic Pain		ysis	**synthetic derivates of THC**, such as dronabinol, nabilone, or benzopyranoperidine (a synthetic nitrogen analog of THC)	of a pathological or traumatic origin	The Cochrane Controlled Trials Register (CENTRAL)				was intensity of pain as scored by numerical rang scales. The Secondary outcomes were CNS related events		for reporting bias, detection bias and for-profit bias			nce suggests that cannabis treatment is moderately efficacious for treatment of chronic pain, but beneficial effects may be partially (or completely) offset by potentially serious harms.
Boyc	The	2015	Syst	**Phytocan**	Neuro	PubMed,	13	771	No	Outcomes	Yes	Yes,	No	No	Cannabis-

huk et. al [24]	Effectiveness of Cannabinoids in the Management of Chronic Nonmalignant Neuropathic Pain: A Systematic Review		ematic Review	**nabinoids;** smoked cannabis, cannabis-based medicinal extracts (CBME) in the form of oromucosal sprays (nabiximols), vaporized cannabis, and **synthetic cannabinoids;** dronabinol, nabilone,	pathic pain	Embase, Web of Science, and all evidence-based medicine reviews and databases (Cochrane Database of Systematic Reviews, ASP Journal Club, Database of Abstracts of Reviews of Effects [DARE], and Cochrane Controlled Trials Register [CCTR])				considered were reduction in pain intensity and adverse events.		except for, reporting bias, publication bias and for-profit bias			based medicinal extracts used in different populations of chronic non-malignant neuropathic pain patients may provide effective analgesia in conditions that are refractory to other treatments.

				and CT-3											
Mücke et. al [26]	Cannabis products for adults with chronic neuropathic pain	2018	Cochrane Review	**Phytocannabinoids;** oromucosal spray containing THC or THC/CBD mix, smoked cannabis containing THC, THC and CBD as extract of cannabis sativa L., and **synthetic cannabinoids;** nabil	Neuropathic pain	Cochrane Library, MEDLINE and EMBASE. Following clinical trials databases were searched for additional data including unpublished data**:** US National Institutes of Health clinical trial register (www.ClinicalTrials.gov), European Union	16 (15 of the trials comparing the intervention with placebo)	1750	Yes	Primary outcomes: Participant-reported pain relief of 50% or greater. We preferred composite neuropathic pain scores over single-scale generic pain scores if both measures were used by studies; PGIC (Patient Global Impres	Yes	Yes	No	Yes	The potential benefits of cannabis-based medicine (herbal cannabis, plant-derived or synthetic THC, THC/CBD oromucosal spray) in chronic neuropathic pain might be outweighed by their

				one, dronabinol		Clinical Trials Register (www.clinicaltrialsregister.eu), World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/), and International Association for Cannabinoid Medicines (IACM) databank (www.cannabis-med.org/studi				sion of Change) much or very much improved; Withdrawals due to adverse events (tolerability); Serious adverse events (safety). Serious adverse events typically include any untoward medical occurrence or effect that at any dose results in death, is life-					potential harms.

						es/study.php)				threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, is an 'important medical event' that may jeopardise the person, or may					

										require an intervention to prevent one of the above characteristics /consequences.					
Aviram et. al [29]	Efficacy of Cannabis-Based Medicines for Pain Management: A Systematic Review and	2017	Meta-Analysis	**Phytocannabinoids;** Sativex/nabiximol, cannabidiol, cannabinoid cigarettes/vaporizer, and **synthetic cannabinoids**; dronabinol and nabil	Chronic (cancer and non-cancer) pain and acute postoperative pain	MEDLINE/Pubmed and in Google Scholar using Medical Subject Heading (MeSH) terms	43 trials comparing the intervention with both 'active drugs' and placebo	2437	No	The outcome measure that was chosen was the variable "pain intensity", as scored by the numerical rating scale (NRS-11), numerical 11-point box (BS-11), visual analog scale (VAS),	Yes	Yes, except for, reporting bias, publication bias and for-profit bias	No	No	The current systematic review suggests that cannabinoid-based medicines might be effective for chronic pain treatment, based on limit

	Meta-Analysis of Randomized Controlled Trials			one, CT-3, ajulemic acid, synthetic nitrogen analog of tetrahydrocannabinol (NIB), fatty acid amide hydrolase-1 (FAAH1) inhibitor (PF-04457845) (blocking degradation of endocannabinoids), benzopyr						and the VAS section of the questionnaire short form McGill Pain Questionnaire.					ed evidence, primarily for neuropathic pain patients.

				anoperidine (BPP), and levonantradol											
Campbell et. al [30]	Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative syste	2001	Systematic Review	Oral THC, an oral synthetic nitrogen analogue of THC (NIB), oral benzopyranoperidine (BPP), and intramuscular levonantradol	Acute, chronic non-malignant pain, and cancer pain	MEDLINE, EMBASE, Oxford Pain Database, and Cochrane Library	9	222	No	Outcome measures for pain intensity; pain relief; the use of supplementary analgesia; patients' preferences; and adverse effects.	Yes	Yes, except for, reporting bias, publication bias and for-profit bias	No	No	Cannabinoids are no more effective than codeine in controlling pain and have depressant effects on the central nervous system that limit their use. Their widespread intro

	matic review														duction into clinical practice for pain management is therefore undesirable. In acute postoperative pain they should not be used.
Deshpande et. al [27]	Efficacy and adverse effects of medical marijuan	2015	Systematic Review	Cigarettes or vaporizer containing delta-9-THC	Neuropathic pain	MEDLINE, EMBASE, and the International Pharmaceutical Abstracts	6 trials comparing intervention with placebo	226	No	For outcomes, pain scores were extracted using the visual analogue scale (VAS) or an alternative	Yes	Yes, except for, reporting bias, publication	No	No	There is evidence for the use of low-dose medical marijuana in refractory neur

	a for chronic noncancer pain						. Placebo being cigarettes or vaporizer containing 0% delta-9-THC or with cannabinoid removal			numerical pain rating tool. If pain scores were not reported, surrogate measures of effectiveness were included (sleep, function, and quality of life). Frequency of serious and most commonly reported adverse effects was collected.		bias and for-profit bias			opathic pain in conjunction with traditional analgesics. However, trials were limited by short duration, variability in dosing and strength of delta-9-tetrahydrocannabinol, and lack of functional outcomes. Altho

															ugh well tolerated in the short term, the long-term effects of psychoactive and neurocognitive effects of medical marijuana remain unknown.
Stevens et. al [31]	A systematic review of the analgesic	2017	Systematic Review	Levonantradol, nabilone, AZD1940, GW842166, dronabinol, △-	Acute postoperative pain	MEDLINE, EMBASE, Cochrane Library, and the World Health Organization Interna	7 trials comparing intervention wit	611	Yes	The primary outcome was the qualitative analysis of the analgesic efficac	Yes	Yes, except for, publication bias	No	Yes	Based on the available randomized controlled trial evidence, cann

	efficacy of cannabinoid medications in the management of acute pain			9-THC		tional Clinical Trials Registry Platform	h placebo, Ketoprofen, Pethidine, Naproxen, and Ibuprofen			y of cannabinoids in the management of acute pain compared to placebo or active comparator. The secondary outcome was the qualitative analysis of the reported adverse effects.		and for-profit bias			abinoids have no role in the management of acute pain.
Walitt et. al [32]	Cannabinoids for fibromyalgia	2016	Cochrane Review	Nabilone	Fibromyalgia	Cochrane Library, MEDLINE and EMBASE	2 trials comparing the interven	72 (40)	Yes	Primary outcomes: Participant-reported pain relief of 50% or	Yes	Yes, except for publication bias.	No	Yes	We found no convincing, unbiased, high quality evidence

							tion with either (1) placebo or (1) amitriptyline			greater. PGIC (Patient Global Impression of Change) much or very much improved. Withdrawal due to adverse events (tolerability). Serious adverse events (safety). Serious adverse events typically include any untoward medical occurrence or					suggesting that nabilone is of value in treating people with fibromyalgia. The tolerability of nabilone was low in people with fibromyalgia.

										effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, is an 'important medical event'					

										that may jeopardise the person, or may require an intervention to prevent one of the above characteristics/consequences.					

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