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Review

Opioid-Sparing Effect of Cannabinoids: A Systematic Review and Meta-Analysis

Suzanne Nielsen*[,1,2], Pamela Sabioni[3], Jose M Trigo[3], Mark A Ware[4], Brigid D Betz-Stablein[5], Bridin Murnion[6,7], Nicholas Lintzeris[2,6], Kok Eng Khor[8], Michael Farrell[1], Andrew Smith[9] and Bernard Le Foll[3]

[1]The National Drug and Alcohol Research Centre, The University of New South Wales, Sydney, NSW, Australia; [2]Drug and Alcohol Services, South Eastern Sydney Local Health District, Surry Hills, NSW, Australia; [3]Translational Addiction Research Laboratory, Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, ON, Canada; [4]Departments of Anaesthesia and Family Medicine, McGill University, Montreal, QC, Canada; [5]School of Public Health and Community Medicine, The University of New South Wales, Sydney, NSW, Australia; [6]Discipline of Addiction Medicine, University of Sydney, Sydney, NSW, Australia; [7]Pain Management Centre, Royal Prince Alfred Hospital, Camperdown, NSW, Australia; [8]Department of Pain Management, Prince of Wales Hospital, Randwick, NSW, Australia; [9]Pain and Addiction Medicine, Centre for Addiction and Mental Health, Toronto, ON, Canada

Cannabinoids, when co-administered with opioids, may enable reduced opioid doses without loss of analgesic efficacy (ie, an opioid-sparing effect). The aim of this study was to conduct a systematic review to determine the opioid-sparing potential of cannabinoids. Eligible studies included pre-clinical and clinical studies for which the outcome was either analgesia or opioid dose requirements. Clinical studies included controlled studies and case series. We searched Scopus, Cochrane Database of Systematic Reviews, Medline, and Embase. Nineteen pre-clinical and nine clinical studies met the search criteria. Seventeen of the 19 pre-clinical studies provided evidence of synergistic effects from opioid and cannabinoid co-administration. Our meta-analysis of pre-clinical studies indicated that the median effective dose (ED_{50}) of morphine administered in combination with delta-9-tetrahydrocannabinol (delta-9-THC) is 3.6 times lower (95% confidence interval (CI) 1.95, 6.76; $n=6$) than the ED_{50} of morphine alone. In addition, the ED_{50} for codeine administered in combination with delta-9-THC was 9.5 times lower (95% CI 1.6, 57.5, $n=2$) than the ED_{50} of codeine alone. One case series ($n=3$) provided very-low-quality evidence of a reduction in opioid requirements with cannabinoid co-administration. Larger controlled clinical studies showed some clinical benefits of cannabinoids; however, opioid dose changes were rarely reported and mixed findings were observed for analgesia. In summary, pre-clinical studies provide robust evidence of the opioid-sparing effect of cannabinoids, whereas one of the nine clinical studies identified provided very-low-quality evidence of such an effect. Prospective high-quality-controlled clinical trials are required to determine the opioid-sparing effect of cannabinoids.
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INTRODUCTION

Chronic pain is associated with enormous personal, social, and economic burden and is the largest contributor to years lived with disability globally (Rice *et al*, 2015). Despite this, existing medications provide only modest relief. Opioids in particular have considerable side effects, including constipation, impaired sleep, and respiratory depression (Chou *et al*, 2015). The last two decades have seen an increase in the prescription of opioids, which has been associated with an increase in opioid use disorders and opioid-related mortality (Chou *et al*, 2015; Volkow and McLellan, 2016; Zedler *et al*, 2014). This has been termed as an 'opioid crisis', and has caused regulators, health professionals, and the public to begin seeking means to reduce problems associated with high-dose opioid use. Consequently, there is a need for evidence-based strategies for reducing reliance on high-dose opioids without compromising pain management.

Using combinations of medications to harness complementary but distinct mechanisms of action can maximize the analgesic response, enabling the use of a lower dose of each medication and resulting in an improved side effect profile. One promising area for medication combinations is the use of opioid-sparing medications. Opioid-sparing medications, when co-administered with opioids, enable a reduced opioid dose without loss of analgesic efficacy. Cannabinoid medications are increasingly being studied for their analgesic- and opioid-sparing potential. The endocannabinoid system represents an ideal target because it is a key endogenous system in modulating pain-processing pathways (Woodhams *et al*, 2015).

The endocannabinoid system is composed of the cannabinoid CB1 and CB2 receptors, the endocannabinoid ligands

*Correspondence: Dr S Nielsen, The National Drug and Alcohol Research Centre, The University of New South Wales, Sydney, NSW 2052, Australia, Tel: +61 2 89361017, Fax: +61 2 9385 0222, E-mail: suzanne.nielsen@unsw.edu.au
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anandamide and 2-arachidonoylglycerol, and their synthesis and degradation system (Pertwee, 2006). CB1 and CB2 receptors are differentially expressed on the central nervous system (Cencioni *et al*, 2010; Herkenham *et al*, 1991) and play important roles in pain processes. Both cannabinoid receptors and endocannabinoids are present in the primary afferent pain circuits to the brain (Manzanares *et al*, 1999; Woodhams *et al*, 2015). Cannabinoid and opioid receptors have similar signal transduction systems (Cichewicz, 2004; Howlett *et al*, 2002; Vigano *et al*, 2005) and are expressed in several brain regions involved in antinociception, including the periaqueductal gray, raphe nuclei, and central-medial thalamic nuclei (Cichewicz, 2004). In addition, mu-opioid receptors and CB1 receptors co-localize in the spinal cord at the first synaptic contact for peripheral nociceptive afferent neurons (Hohmann *et al*, 1999; Salio *et al*, 2001).

It has previously been observed that CB2 receptors indirectly stimulate opioid receptors located in primary afferent pathways (Ibrahim *et al*, 2005). Therefore, in addition to their direct analgesic effects, cannabinoids may work synergistically to enhance opioid analgesia. The behavioral, anatomical, and biochemical similarities between opioid and cannabinoid receptor systems and their endogenous ligands are well documented. For example, activation of either cannabinoid or opioid receptors produces comparable neurobehavioral and physiological effects, including antinociception (Manzanares *et al*, 1999). This is highlighted by both CB1 and CB2 agonists being able to induce antinociception by increasing opioid precursors' gene expression or via release of endogenous opioids (Houser *et al*, 2000; Ibrahim *et al*, 2005; Valverde *et al*, 2001). Further, pharmacological modulation of the opioid system can modify the effects of delta-9-tetrahydrocannabinol (delta-9-THC)—a partial agonist at the CB1 and CB2 receptor—on nociception (Mason *et al*, 1999; Pugh *et al*, 1997; Smith *et al*, 1994) and *vice versa*. Finally, cannabinoid antagonists have been shown to reverse the antinociception induced by morphine (da Fonseca Pacheco *et al*, 2008). Collectively, this strongly supports shared mechanisms between both systems in regard to analgesia.

Animal models have identified a role for CB1 receptor activation in reducing neuropathic, visceral, and inflammatory pain (Pertwee, 2008; Walker *et al*, 1999). Several pre-clinical studies have demonstrated that systemic administration of cannabinoid receptor ligands produces analgesia in acute and chronic pain models (Walker and Huang, 2002). In addition, the role of CB2 receptors has been explored in pre-clinical studies, suggesting that these receptors may mediate effects in inflammatory pain states (Ibrahim *et al*, 2006; Quartilho *et al*, 2003), and reduce inflammation and neuropathic pain (Gui *et al*, 2015).

Further to these pre-clinical findings, clinical studies indicate that cannabinoid administration may reduce pain and improve other symptoms such as sleep disturbances associated with chronic pain (Ware *et al*, 2010a; Ware *et al*, 2010b). This effect could be mediated by delta-9-THC, which is the main psychoactive ingredient present in cannabis (Cichewicz, 2004; Jensen *et al*, 2015). Despite the growing body of relevant literature, to date no systematic review has focused on the opioid-sparing effects of cannabinoids. To address this gap, we conducted a systematic review of pre-clinical and clinical studies to examine the strength of existing evidence demonstrating the opioid-sparing effect of cannabinoids in the context of analgesia.

MATERIALS AND METHODS

Search

We conducted a systematic search of the literature in accordance with recommendations by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher *et al*, 2009). The search aimed to identify clinical and pre-clinical studies using the following electronic databases: Scopus, Cochrane Database of Systematic Reviews, Medline, and Embase. Search terms are listed and a sample search strategy is reported in Supplementary Appendix 1. No date limits were included. Searches were run on 29 October 2015. In addition, reference lists from identified studies and review articles were searched to find additional studies not identified by the main search.

Eligible studies included:

- Human or animal studies.
- Outcomes of either pain/analgesia or opioid requirements/opioid-sparing effects from concurrently administered opioids and cannabinoids.
- Controlled clinical studies and case series.

Titles were screened by two authors (SN and PS). Where inconsistencies were identified, the authors were able to reach consensus on each occasion.

Data Extraction and Outcomes

Data extraction forms were developed and circulated to the author group before piloting and refining. All data were extracted by one of the authors (SN, PS, or JMT) and checked by a second author (SN, PS, or JMT). These same authors reviewed and resolved any inconsistencies, with input from the authorship group as required. When required data were missing, attempts were made to contact authors of published reports to collect additional information.

Outcome Measures

For pre-clinical studies, the primary outcome was the dose of opioid required to give an equivalent antinociceptive effect in the presence and absence of cannabinoids. For clinical studies, the primary outcome was evidence of the opioid-sparing effect of cannabinoids. Data were extracted on opioid dose and/or analgesic outcome where cannabinoids were co-administered. Secondary outcome measures examined included analgesia, sleep, and quality of life.

Analysis

Pre-clinical studies. Data were extracted and a narrative review was conducted. Ten studies were identified as sufficiently similar in design and outcome measures to be eligible for meta-analysis. Of these, six reported sufficient data to enable meta-analysis; that is, the dose of opioid required to produce comparable analgesia in the presence and absence of cannabinoids, the variance of the observed dose, and the sample size. Authors of the other studies were

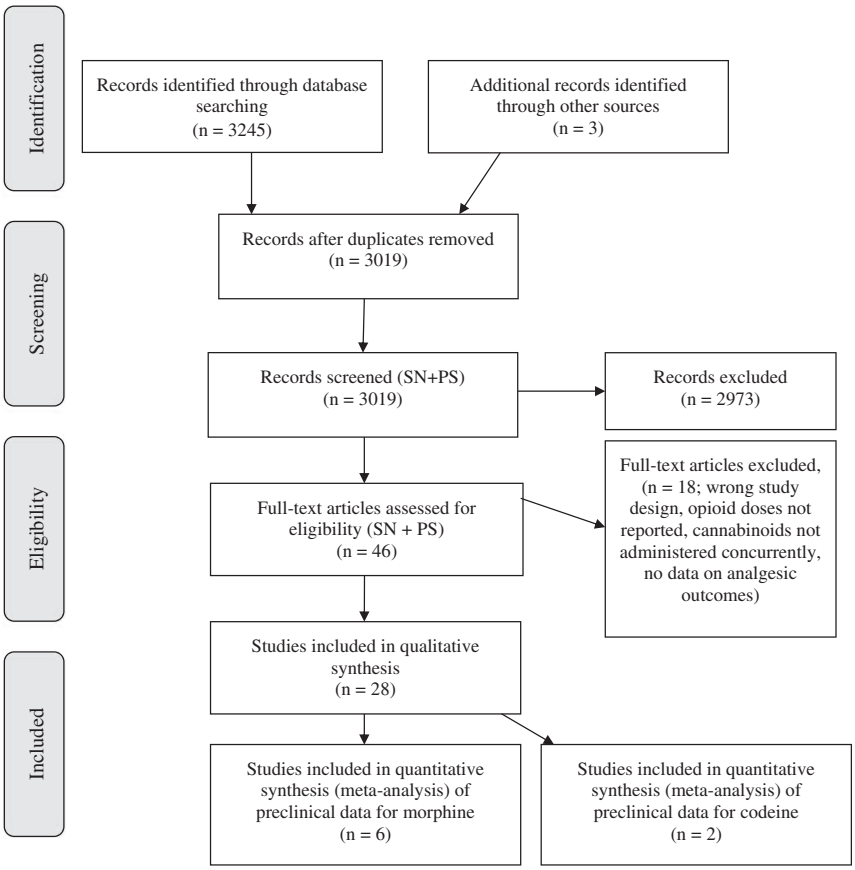

Figure 1 PRISMA diagram showing study identification. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

contacted in an attempt to include additional studies in the meta-analysis; however, no additional data were identified to enable the inclusion of any additional studies.

To prepare the data for the meta-analysis, the effective dose (ED_{50}) and either confidence limits or SE were extracted from the relevant literature. ED_{50} is calculated on the $\log_{10}$ scale. Therefore, to meet the assumption of normality, the $\log_{10}\widehat{ED}_{50}$ must be used in the meta-analysis. The $\log_{10}$ of the confidence limits must also be determined to calculate the SD of the $\log_{10}\widehat{ED}_{50}$:

$$\mathrm{SD}\left(\log_{10}\widehat{\mathrm{ED}}_{50}\right) = \frac{\log_{10}\mathrm{UL} - \log_{10}\widehat{\mathrm{ED}}_{50}}{1.96},$$

where UL is the upper confidence limit.

When only SE was reported, the confidence limits were calculated using the method of Litchfield and Wilcoxon (1949) and the above procedure was repeated to calculate the SD. This method also allowed for the inclusion of studies that did not report exact sample sizes for all treatment groups, as sample size was not required for the calculation of SD.

Data for the meta-analysis were analyzed using Review Manager 5.1 (Cochrane Collaboration, Oxford, UK). When calculating the continuous outcome of an equally effective opioid dose (eg, the $\log_{10}ED_{50}$ for morphine when administered alone *vs* when administered with a cannabinoid), the inverse variance statistical method and random effects model were used to compensate for study heterogeneity.

No statistical difference was found in outcomes between the studies that used different species or nociceptive assays. Therefore, the mean difference of $\log_{10}ED_{50}$ of and the corresponding 95% confidence intervals (CI) were calculated. Due to the nature of log calculations, the mean difference—when back-transformed to the original units—represents the response ratio. For easier interpretation, we present the reciprocal of the response rate.

Assessment of bias in pre-clinical studies. A funnel plot was produced to examine publication bias and small study effects in the pre-clinical studies included in the meta-analysis.

Clinical studies. The nine clinical studies identified were heterogeneous in design and outcomes, and therefore not suitable for meta-analysis. Thus, a narrative synthesis was conducted instead, with all studies scored for quality using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria (Guyatt *et al*, 2008).

RESULTS

The initial searches identified 3019 records after duplicates were removed, with 19 pre-clinical and nine clinical studies identified for inclusion in the final review (see Figure 1 for the PRISMA diagram).

Table 1 Summary of Evidence of Opioid-Sparing Effects from Pre-Clinical Studies

		Equipotent opioid dose represented as ED_{50}(95% CL) or ± SEM, unless measured otherwise specified					
Study reference	**Pain model (species)**	**Opioid administered**	**Cannabinoid administered**	**Cannabinoid condition**	**Vehicle condition**	**Potency ratio or evidence of synergism**	**Other notes**
Cichewicz *et al*, 1999	Tail-flick test (male ICR mice)	Morphine p.o.	Delta-9-THC (20 mg/kg p.o.)	13.1 mg/kg (8.8, 19.5)	28.8 mg/kg (20.2, 41)	Potency ratio: 2.2	
		Codeine p.o.	Delta-9-THC (20 mg/kg p.o.)	5.9 mg/kg (1.4, 24.9)	139.9 mg/kg (75.2, 260.5)	Potency ratio: 25.8	
		Oxymorphone p.o.	Delta-9-THC (20 mg/kg p.o.)	0.5 mg/kg (0.3, 0.8)	2.6 mg/kg (1.7, 3.9)	Potency ratio: 5.0	
		Hydromorphone p.o.	Delta-9-THC (20 mg/kg p.o.)	0.4 mg/kg (0.2, 0.8)	5.6 mg/kg (3.2, 9.7)	Potency ratio: 12.6	
		Methadone p.o.	Delta-9-THC (20 mg/kg p.o.)	2.7 mg/kg (1.4, 5.2)	12.0 mg/kg (8.1, 17.9)	Potency ratio: 4.1	
		LAAM p.o.	Delta-9-THC (20 mg/kg p.o.)	2.6 mg/kg (1.7, 3.9)	8.0 mg/kg (6.4, 10.1)	Potency ratio: 2.5	
		Heroin p.o.	Delta-9-THC (20 mg/kg p.o.)	5.4 mg/kg (1.7, 16.9)	26.1 mg/kg (12.7, 53.4)	Potency ratio: 4.1	
		Meperidine p.o.	Delta-9-THC (20 mg/kg p.o.)	11.1 mg/kg (4.2, 29.4)	86.2 mg/kg (52.8, 140.6)	Potency ratio: 8.9	
		Fentanyl p.o.	Delta-9-THC (20 mg/kg p.o.)	0.5 mg/kg (0.3, 0.8)	6.1 mg/kg (estimated from an extrapolated curve)	Not determined (50% MPE not seen)	
		Pentazocine p.o.	Delta-9-THC (20 mg/kg p.o.)	838.6 mg/kg (estimated from an extrapolated curve)	625.9 mg/kg (estimated from an extrapolated curve)	Not determined (50% MPE not seen)	
Cichewicz and Welch, 2003	Tail-flick test (male ICR mice)	Morphine p.o. Codeine p.o.	Delta-9-THC (5–35 mg/kg and 1–27 mg/kg p.o.)	13.6 mg/kg ± 1.94	24.5 mg/kg ± 4.8 78.2 mg/kg ± 14.4	For each ratio tested, experimental values were less than the calculated additive values (synergism)	Fixed-ratio combinations of 9-THC with either morphine or codeine were tested for antinociceptive effects. The experimentally derived ED_{50} for each combination was compared with the theoretical additive ED_{50}, using an isobolographic analysis. All the fixed-ratio combinations tested produced greater antinociception (synergy) than predicted from simple additivity
			Delta-9-THC (5–30 and 5–18 mg/kg p.o.)	20.1 mg/kg ± 3.0		For each ratio tested, experimental values were less than the calculated additive values (synergism)	
Cichewicz *et al*, 2005	Pin-prick test (IAF hairless guinea pigs)	Fentanyl s.c.	Delta-9-THC (50 mg/kg i.p.)	6.8 μg/kg (3.3, 14.2)	50.8 μg/kg (41.0, 63.0)	Greater than additive effect on antinociception. Potency ratio: 6.7 (1.8–17.0)	
		Buprenorphine s.c.	Delta-9-THC (50 mg/kg i.p.)	0.02 mg/kg (0.01, 0.05)	2.97 mg/kg (1.84, 4.81)	Greater than additive effect on antinociception. Enhanced potency in a non-parallel fashion	Not possible to compare the change in potency produced by delta-9-THC due to the non-parallel nature of the two dose–response curves for buprenorphine
		Fentanyl t.d.	Delta-9-THC (400 mg/kg t.d.)	2 h: 254.9 μg/kg (202.90, 320.6) 4 h: 176.3 μg/kg (144.3, 215.5)	2 h: 928.6 μg/kg (599.5, 1438.3) 4 h: 1067.0 μg/kg (840.4, 1356.1)	Potency ratio at 2 h: 3.7 Potency ratio at 4 h: 5.8	
		Buprenorphine t.d.	Delta-9-THC (400 mg/kg t.d.)	2 h: 4.3 mg/kg (2.8, 6.8) 4 h: 2.2 mg/kg (1.1, 4.6)	2 h: 26.1 mg/kg (17.1, 39.9) 4 h: 15.6 mg/kg (10.0, 24.5)	Potency ratio at 2 h: 8.2 Potency ratio at 4 h: 7.2	
Cox *et al*, 2007	Paw pressure test (Male Sprague–Dawley rats)	Morphine i.p. (normal rats) Morphine i.p. (arthritic rats)	Delta-9-THC (0.4 mg/kg ± 0.5 i.p.) (1 : 1 ratio THC : Morphine) Delta-9-THC (0.6 mg/kg ± 0.55 i.p.) (1 : 1 ratio THC : Morphine)	0.4 mg/kg ± 0.5 0.6 mg/kg ± 0.55	2.4 mg/kg (2.2, 2.8) 2.2 mg/kg (1.9, 2.4).	The combination of delta-9-THC and morphine showed synergism in both non-arthritic and arthritic rats	Results from normal rats included in the meta-analysis only
Finn *et al*, 2004	Formalin-evoked nociceptive behavior (adult male Lister-Hooded rats)	Morphine i.p.	Delta-9-THC (1 mg/kg i.p.)	Not reported	Not reported	Not clearly synergistic. Potentially additive. Morphine (2 mg/kg) + delta-9-THC (1 mg/kg) had a significant effect on nociceptive behavior (compared to morphine alone but not delta-9-THC alone).	

Table 1 Continued

Equipotent opioid dose represented as ED_{50}(95% CL) or ± SEM, unless measured otherwise specified							
Study reference	**Pain model (species)**	**Opioid administered**	**Cannabinoid administered**	**Cannabinoid condition**	**Vehicle condition**	**Potency ratio or evidence of synergism**	**Other notes**
Katsuyama *et al*, 2013	Capsaicin test (Male mice of ddY strain)	Morphine (1.0 mg/kg s.c. and 100 pmol i.t.)	Beta-caryophyllene (2.25 mg i.pl., CB2 receptor agonist)	ID_{50} 1.16 mg/kg (1.03, 1.32, systemic, s.c.) and 130.1 pmol (111.9, 156.4, spinal, i.t.)	ID_{50} 2.51 mg/kg (2.17, 2.97) (systemic, s.c.) and 193.7 pmol (165.7, 225.6, spinal, i.t.)	Morphine + beta-caryophyllene decreased licking/biting response $p<0.05$ compared to morphine + saline or beta-caryophyllene + jojoba wax.	Ineffective doses of beta-caryophyllene significantly enhanced morphine-induced antinociception.
Li *et al*, 2008	Thermal antinociception (rhesus monkeys)	Morphine s.c.	Delta-9-THC (0.32 and 1.0 mg/kg s.c.)	ED_{80} 2.42 mg/kg	ED_{80} 6.36 mg/kg (3.81, 8.91)	Pre-treatment with delta-9-THC enhanced the antinociceptive effects of morphine.	Morphine dose dependently increased the latency for monkeys to remove their tails from 50°C and 55°C water.
Maguire *et al*, 2013	Warm water tail withdrawal (rhesus monkeys)	Morphine s.c.	CP 55 940 (0.01 mg/kg s.c.) WIN 55 212 (0.32 mg/kg s.c.)	Mean ($n=3$) CP 0.23 mg/kg WIN 0.24 mg/kg	1.26 mg/kg (mean, $n=3$)	Pre-treatment with CP 55 940 resulted in a mean leftward shift to of –6.73-fold. Pre-treatment with WIN 55 212 resulted in mean leftward shift of –5.5-fold.	Antinociception from the combination appeared to be achieved without an increase in abuse liability.
Pugh *et al*, 1996	Tail-flick test (mail ICR mice)	Morphine i.t.	Delta-9-THC (6 µcg/mouse i.t., inactive analgesic dose)	0.01 mcg/mouse	0.318 mcg/mouse (2.825, 0.036)	Greater than additive effect observed, clear leftward shift of graph.	
Reche *et al*, 1996	Tail-flick and hot plate test (Swiss albino mice)	Morphine i.p.	Delta-9-THC i.p.	NA Only one dose of morphine (2 mg/kg i.p.) examined. Study measured change in ED_{50} of delta-9-THC.	NA	Morphine pre-administration shifted the dose–response curve for delta-9-THC to the left (a 2.5-fold shift for the tail-flick test and a three-fold shift for the hot plate test). Analgesic effect blocked by SR-141 716 (cannabinoid antagonist) and naloxone.	
Smith *et al*, 1998	Tail-flick and hot plate test (male ICR mice)	Morphine s.c.	Tail-flick: delta-9-THC (4 mg/kg s.c.)	0.29 mg/kg (95% CI 0.04, 1.94)	2.81 mg/kg (2.24, 3.53)	Potency ratio: 8.5	Multiple conditions tested different combinations of s.c and p.o morphine. Only s.c. + s.c. and p.o. + p.o. for the tail-flick test are reported here. A paw withdrawal test was also conducted to demonstrate that enhancement of antinociception was not limited to the tail.
		Morphine p.o.	Tail-flick: delta-9-THC (20 mg/kg p.o.)	2.8 mg/kg (2.0, 3.9)	31.7 mg/kg (22.4, 44.9)	Potency ratio: 7.6	
Smith *et al*, 2007	Paw withdrawal test (male Sprague–Dawley rats)	Morphine s.c.	Delta-9-THC (0.75 mg /kg i.p.)	ED_{80} morphine + delta-9-THC (0.75 mg/kg)	ED_{80} morphine alone (100 mg/kg)	Tolerance to morphine alone rapidly established; no loss of effect with low-dose combinations of morphine + delta-9-THC	A morphine pellet arm and delta-9-THC alone arm were not reported in this table due to difficulties in comparing doses between morphine formulations.
Tham *et al*, 2005	Tail-flick and hot plate test (Swiss male mice)	Morphine s.c.	Tail-flick: CP 55 940 (0.1–3 mg/kg s.c.) Hot plate: CP 55 940 (0.1–3 mg/kg s.c.)	3.31 mg/kg 7.54 mg/kg	11.3 mg/kg (9.6, 13.4) 29.4 mg/kg (27.3, 31.6)	Analyses showed greater than additive results (synergism).	
Wakley and Craft, 2011	Paw pressure test (male Sprague–Dawley rats)	Methadone i.p.	Delta-9-THC (0.32–3.2 mg/kg i.p.)	Not reported (dose–response curve shown)	ED_{50} in naive rats, 1.27 mg/kg (95% CI 0.91, 1.91), ED_{50} in rats trained for discrimination, 3.49 mg/kg (95% CI 2.59, 5.31)	In opioid and delta-9-THC naive rats, methadone 1.0 mg/kg significantly enhanced the antinociceptive effect of delta-9-THC, however this was not observed in rats that were previously trained for drug discrimination tasks.	The rats trained for drug discrimination tasks had received repeated administration of opioids and cannabinoids over many months and may have been tolerant to drug effects at the doses administered.
Welch and Stevens, 1992	Tail-flick and hot plate test (mice)	Morphine i.t.	Delta-9-THC (3.133 mcg/mouse)	0.15 mcg/mouse (0.11, 0.21)	0.61 mcg/mouse (0.26, 1.44)	Yes	
			Delta-9-THC (6.25 mcg/mouse)	0.05 mcg/mouse (0.03, 0.08)		Yes	

Table 1 Continued

Equipotent opioid dose represented as ED_{50}(95% CL) or ± SEM, unless measured otherwise specified							
Study reference	**Pain model (species)**	**Opioid administered**	**Cannabinoid administered**	**Cannabinoid condition**	**Vehicle condition**	**Potency ratio or evidence of synergism**	**Other notes**
			Delta-8-THC (25 mcg/mouse)	0.05 mcg/mouse (0.02, 0.10)		Yes	
			Levonantradol (0.005 mcg/mouse)	0.06 mcg/mouse (0.01, 0.24)		Yes	
			CP 55 940 (0.01 mcg/mouse)	0.3 mcg/mouse (0.0, 0.10)		Additive	
			CP 56 667 (0.5 mcg/mouse)	0.26 mcg/mouse (0.08, 0.82)		Additive	
			11-hydroxy-delta-9-THC (3 mcg/mouse)	0.08 mcg/mouse (0.04, 0.19)		Yes	
			Dextronantradol (25 mcg/mouse)	0.51 mcg/mouse (0.36, 0.89)		No	
Williams *et al*, 2006	Tail-flick test (mail ICR mice)	Study 1: low-dose codeine (30 mg/kg) and morphine (20 mg/kg) and fully efficacious ED_{80}, codeine (100 mg/kg) and morphine (80 mg/kg). Study 2: high-dose codeine (200 mg/kg) and morphine (100 mg/kg) (all p.o.)	Delta-9-THC (20 mg/kg p.o., inactive analgesic dose)	ED_{80} codeine (30 mg/kg) ED_{80} morphine (20 mg/kg)	ED_{80} codeine (200 mg/kg) ED_{80} morphine (100 mg/kg)	A low dose of morphine (20 mg/kg) or codeine (30 mg/kg) with a single pre-treatment of an inactive dose of delta-9-THC produced the same efficacy (ED_{80}) as the high doses of each opioid alone. For codeine, delta-9-THC pre-treatment also increased the duration of action of the ED_{80} dose of codeine.	Study 1: pre-treatment with delta-9-THC did not enhance the fully efficacious dose of morphine but enhanced low-dose morphine and both doses of codeine, in addition to extending the time course. Study 2: delta-9-THC restored analgesic efficacy after the time that the opioids had ceased being effective on their own (360 min post dose for morphine and 120 min post dose for codeine).
Williams *et al*, 2008	Tail-flick test (diabetic and non-diabetic mice and rats)	Morphine s.c. Morphine s.c.	Delta-9-THC (20 mg/kg p.o.) in non-diabetic mice Delta-9-THC (20 mg/kg p.o.) in diabetic mice	2.5 mg/kg (1.8, 3.4) 0.84 mg/kg (0.79, 0.89)	5.6 mg/kg (4.3, 7.2) 6.1 mg/kg (5.2, 7.1)	Yes Yes	Delta-9-THC significantly enhanced morphine-induced antinociception in both diabetic and non-diabetic mice.
Wilson *et al*, 2008	Hot plate test (male Sprague–Dawley rats)	Morphine microinjections into PAG	HU-210 (5 μg)	Not reported (dose–response curve shown)	Not reported (dose–response curve shown)	No evidence of synergism. Morphine + HU-210 showed the greatest increase in hot plate latency (39.9 s ± 1.1 s), but was not significantly different from morphine alone (33.1 s ± 4.0 s)	HU-210 shown to prevent development of tolerance to morphine's antinociceptive effects. HU-210 pre-treatment enhanced subsequent morphine antinociception. Co-administration of HU-210 into the PAG attenuated morphine antinociception. The authors suggested that opioids and cannabinoids may have opposing actions within the PAG.
Yesilyurt *et al*, 2003	Tail-flick test (adult female Bulb-C mice)	Morphine topical	WIN 55, 212-2 (20 mg/ml, topical, mixed CB1-CB2 receptor agonist)	Morphine (20 mg/ml) + WIN sustained analgesic effect of 50% analgesia over 4 h	Morphine (20 mg/ml) alone produced 18% analgesic effect, peak at 20 min then reduced.	Antinociceptive effects were markedly potentiated (they peaked and were sustained at 30 min) compared to morphine response alone.	

Abbreviations: delta-9-THC, delta-9-tetrahydrocannabinol; ED, effective dose; ICR, imprinting control region; ID, inhibitory dose; i.p., intraperitoneal; i.t., intrathecal; MPE, maximum possible effect; PAG, periaqueductal gray matter; pmol, picomol; p.o., oral administration; s.c., subcutaneous; t.d, transdermal.

Summary of Pre-Clinical Studies

Nineteen pre-clinical studies were identified in which the analgesic effect of opioid and cannabinoid co-administration was examined (Cichewicz *et al*, 1999, 2005; Cichewicz and McCarthy, 2003; Cox *et al*, 2007; Finn *et al*, 2004; Katsuyama *et al*, 2013; Li *et al*, 2008; Maguire *et al*, 2013; Pugh Jr *et al*, 1996; Reche *et al*, 1996; Smith *et al*, 1998, 2007; Tham *et al*, 2005; Wakley and Craft, 2011; Welch and Stevens, 1992; Williams *et al*, 2006, 2008; Wilson *et al*, 2008; Yesilyurt *et al*, 2003) (Table 1). Fourteen of these studies examined delta-9-THC, whereas one to two studies examined each of 10 other cannabinoid agonists, including beta-caryophyllene, CP 55 940, CP 56 667, delta-8-THC, 11-hydroxy-delta-9-THC, dextronantradol, levonantradol, WIN 55, 212-2, and HU-210. Seventeen studies examined morphine, three studies examined codeine, and one to two studies examined buprenorphine, fentanyl, oxycodone, morphine, hydromorphone, methadone, LAAM, meperidine, and pentazocine. Most of the studies used rodents; however, two used rhesus monkeys and one used guinea pigs. The most common antinociceptive assays were tail-flick tests ($n=10$) and hot plate tests ($n=5$), although individual studies also used other forms of mechanical, thermal, and chemical nociception.

Most studies (17 of the 19) demonstrated that combining a cannabinoid with an opioid resulted in a synergistic effect on analgesia compared to the analgesic effects of the individual drugs. One study examined a single dose of morphine and demonstrated that morphine could potentiate the analgesic effect of intrathecally administered delta-9-THC (Reche *et al*, 1996). However, this study could not demonstrate an opioid-sparing effect due to the use of a single dose of opioid. Another study found that 2 mg/kg morphine administered with 1 mg/kg delta-9-THC resulted in a significant effect on nociception compared to morphine alone ($p<005$), but not when compared to delta-9-THC alone (Finn *et al*, 2004). In another study, a greater increase in hot plate latency was found for morphine combined with HU-210 (38.9 s ± 1.1 s) compared with HU-210 alone (33.1 s ± 4.0 s) (Wilson *et al*, 2008); however, this difference did not reach significance.

One study testing multiple opioid agonists identified clear synergistic effects for delta-9-THC for most opioid drugs, with the exception of fentanyl and pentazocine (Cichewicz *et al*, 1999). The potency ratio when administered alone for those opioids found to have a synergistic effect, compared to when those same opioids were co-administered with delta-9-THC varied between 2.2 and 25.8. Another study tested multiple cannabinoid agonists when co-administered with morphine and demonstrated a synergistic effect with delta-9-THC, delta-8-THC, levonantradol, and 11-hydroxy-delta-9-THC; additive effects with CP 55 940 and CP 56 667; and no observable potentiation of morphine effects with dextronantradol, which is an isomer of levonantradol (Welch and Stevens, 1992). In contrast to the finding of an additive effect for CP 55 940, two other studies of CP 55 940 in combinations with morphine demonstrated a synergistic analgesic effect (Maguire *et al*, 2013; Tham *et al*, 2005). In addition to changes in the magnitude of the analgesic effect, two studies showed that the duration of the analgesic effect can be extended by administrating a low-dose opioid and cannabinoid in combination, compared with administrating an opioid alone (Williams *et al*, 2006; Yesilyurt *et al*, 2003).

Meta-Analysis of Pre-Clinical Studies

Six studies used sufficiently similar approaches to enable a meta-analysis (Cichewicz *et al*, 1999; Cichewicz and Welch, 2003; Cox *et al*, 2007; Smith *et al*, 1998; Welch and Stevens, 1992; Williams *et al*, 2008) (Figure 2). A further four studies were comparable in study design, but did not contain the required data (ED_{50} or variance on estimates) to enable meta-analysis (Finn *et al*, 2004; Pugh Jr *et al*, 1996; Smith *et al*, 2007; Williams *et al*, 2006). All studies included in the meta-analysis used rodents and reported comparable antinociceptive doses of morphine alone and morphine co-administered with delta-9-THC. Results from the meta-analysis are reported in terms of mean difference.

The meta-analysis identified a significant opioid-sparing effect with morphine and delta-9-THC co-administration, $Z=5.59$, $p<0.001$ (MD in $\log_{10}ED_{50}$ −0.56 (−0.83, −0.29)). As there was significant heterogeneity in the data ($I^2=95\%$), a random effects model was used. When back-transformed to the original units, the response ratio was 3.6 (95% CI 1.95, 6.76), indicating that the median ED_{50} of morphine was 3.6 times lower when given in combination with delta-9-THC compared to when morphine was administered alone.

Two studies compared doses of codeine with and without delta-9-THC in rodents (Cichewicz *et al*, 1999; Cichewicz and Welch, 2003) (Figure 3). Both studies used male ICR mice and the tail-flick assay. Meta-analysis of these data indicated a significant opioid-sparing effect of delta-9-THC when co-administered with codeine, $Z=2.49$, $p=0.01$

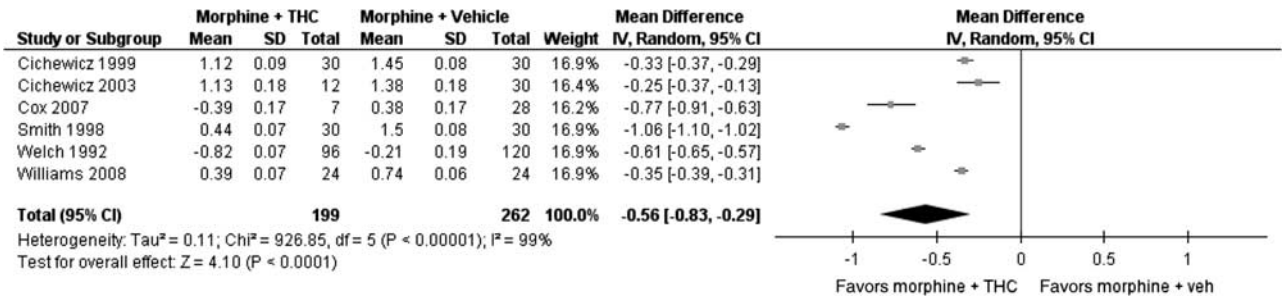

Figure 2 Forrest plot for meta-analysis examining the opioid-sparing effect of delta-9-THC when co-administered with morphine. Note: all mean difference and SD values are of $\log_{10}ED_{50}$. THC, tetrahydrocannabinol.

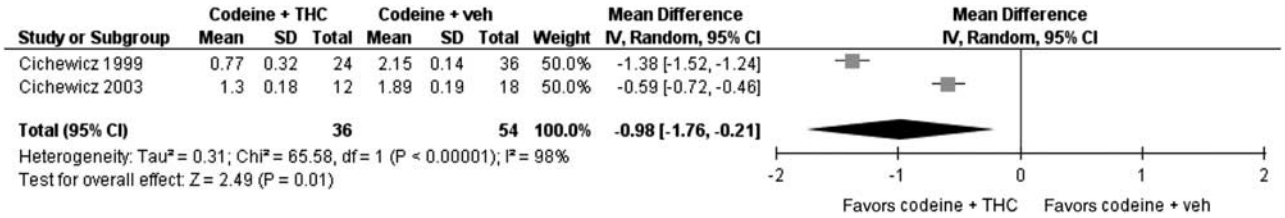

Figure 3 Forrest plot for meta-analysis examining the opioid-sparing effect of delta-9-THC when co-administered with codeine. Note: all mean difference and SD values are of $\log_{10}ED_{50}$. THC, tetrahydrocannabinol.

(MD in the $\log_{10}ED_{50}$ −0.98 (−1.76, −0.21)). Significant heterogeneity in the data ($I^2 = 98\%$) necessitated the use of a random effects model. When back-transformed to the original units, the response ratio was 9.5 (95% CI 1.6, 57.5), indicating that the ED_{50} of codeine was 9.5 times lower when given in combination with delta-9-THC compared to when codeine was administered alone.

Funnel plots did not provide evidence of publication or small study bias with these pre-clinical studies (Figure 4).

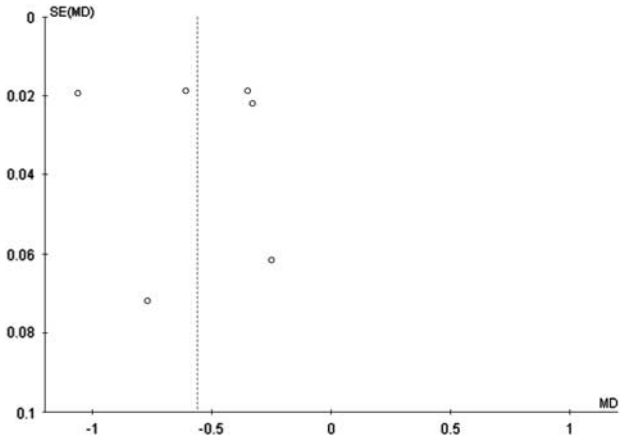

Figure 4 Funnel plot showing data from the six studies included in the meta-analysis. MD, mean difference, SE, standard error.

Results from Clinical Studies

Nine clinical studies with 750 participants provided data relevant to the research question (Table 2); however, the heterogeneous nature of the studies precluded meta-analysis. Three laboratory-based studies examined pain responses in participants concurrently being administered opioids and cannabinoids. One study recruited people with mixed chronic non-cancer pain ($n = 24$) who were prescribed opioids (Abrams *et al*, 2011). A significant reduction in pain ratings was observed for the participants in this study following co-administration of cannabinoids—39.6 (95% CI 35.8, 43.3) at baseline *vs* 29.1 (95% CI 25.4, 32.8) following co-administration (Abrams *et al*, 2011). It should be noted that no placebo or control condition was used in this study for comparison (Abrams *et al*, 2011).

In another two studies, healthy volunteers ($n = 12$ and 13, respectively) participated in crossover studies, with single doses of placebo, morphine alone, dronabinol alone, and dronabinol and morphine combined administered over four sessions (Naef *et al*, 2003; Roberts *et al*, 2006). These studies did not identify a synergistic effect on experimental pain in healthy controls, although Roberts *et al* (2006) found that the co-administration of dronabinol and morphine resulted in a reduced unpleasantness of pain compared to either drug alone. In a case series examining the effects of cannabinoid administration in patients with chronic non-cancer pain, three patients with mixed pain conditions (multiple sclerosis, HIV-related peripheral neuropathy, and lower back and leg pain) reported reductions in opioid requirements after initiation of smoked cannabis plant material (Lynch and Clark, 2003).

Five controlled studies were identified. One small, non-randomized study of patients with advanced cancer pain found that 5 out of 12 patients achieved pain control after receiving a cannabis infusion, compared with 2 out of 14 achieving pain control in the control group—a non-statistically different effect (Lissoni *et al*, 2014). Two randomized controlled trials examined delta-9-THC : Cannabidiol (THC : CBD) combination oral sprays compared to a placebo (Johnson *et al*, 2010; Portenoy *et al*, 2012) in patients with cancer pain who were taking opioids. These studies found improved analgesia with the THC : CBD combination compared to the placebo. Johnson *et al* (2010) found no effect of THC : CBD on breakthrough opioid dose requirements. Portenoy *et al* (2012) conducted a dose-ranging study, using fixed dose ranges of the THC : CBD combination. In this study, a significant analgesic effect was only found in the lowest dose group, with poorer tolerability observed for higher doses.

Two controlled studies examined the effects of dronabinol: one in patients with mixed chronic pain (Narang *et al*, 2008) and one in patients with prostate cancer (Seeling *et al*, 2006). Narang *et al* (2008) found significantly reduced pain intensity with the opioid–cannabinoid combination in double-blinded laboratory sessions compared to opioid alone. Additional improvements in sleep, energy, and social functioning were reported in a 4-week open-label phase of the same study (Narang *et al*, 2008). In the study by Seeling *et al* (2006), perioperative use of dronabinol compared with a placebo in patients with prostate cancer, no difference was found in self-administered opioid dose requirements between groups.

Quality Ratings of Clinical Studies

The clinical studies were rated using the GRADE criteria. One study provided very-low-quality evidence, three studies provided low-quality evidence, two studies provided moderate-quality evidence, and three randomized controlled

Table 2 Summary of Evidence of Opioid-sparing Effects from Clinical Studies

(a) Study reference	Study design	Population	Follow-up period	Opioid used	Cannabinoid used	Effect of cannabinoid on opioid dose	Outcome on analgesia observed	GRADE evidence rating and other notes
Laboratory studies								
Abrams *et al*, 2011	Clinical laboratory study of self-reported pain under observed conditions (also measured pharmacokinetic effects of concurrent administration)	People ($n=24$) receiving chronic opioid treatment (mixed pain conditions)	5 days	Morphine sulfate (mean daily dose 62 mg, $n=13$) or oxycodone hydrochloride (mean daily dose 53 mg, $n=11$)	Vaporized cannabis dose of 0.9 g of 3.56% delta-9-THC or as much as they could tolerate, administered three times per day.	Opioid dose held constant to examine effect of delta-9-THC on opioid pharmacokinetics (ie, no reduction from baseline opioid dose possible).	Mean pain score reduction, from 34.8 (95% CI 29.4, 40.1) at baseline to 24.1 (95% CI 18.8, 29.4) on day 5 with morphine, and from 43.8 (95% CI 38.6, 49.1) at baseline to 33.6 (95% CI 28.5, 38.6) on day 5 with oxycodone. Significant reduction overall.	Cannabis inhalation produced a subjective 'high'. GRADE rating 'low' quality. Downgraded as study did not have a placebo condition, so placebo effects cannot be excluded Note: no pharmacokinetic interaction observed.
Naef *et al*, 2003	Experimental heat, cold, pressure, single and repeated transcutaneous electrical stimulation pain, randomized, placebo-controlled, double-blinded, crossover study.	Healthy cannabis naive volunteers ($n=12$)	Four study sessions with at least 7 days washout between sessions	Morphine (30 mg) daily	Dronabinol (20 mg)	No significant analgesic effect of dronabinol or morphine–dronabinol combination on heat, pressure, or cold tests. Additive effect of morphine on transcutaneous electrical stimulation test.	Potentiation of analgesia not observed in this experimental pain study.	GRADE rating 'moderate'. Placebo-controlled, blinded study. Downgraded due to indirect evidence as use of experimental pain measures.
Roberts *et al*, 2006	Experimental thermal pain. Double-blinded, four treatment crossover design.	Healthy volunteers ($n=13$) with no recent opioid or cannabinoid use	Four lab sessions	Morphine (0.02 mg/kg IV, 1.4 mg dose for 70 mg adult, ie, sub-analgesic)	Dronabinol (5 mg)	NA (opioid dose held constant)	Combination of delta-9-THC and morphine did not have an effect on pain intensity. The combination resulted in lower ratings of unpleasantness of pain compared with either drug alone.	GRADE rating 'moderate'. Placebo-controlled, blinded study. Downgraded due to indirect evidence as use of experimental pain measures.
Case series								
Lynch and Clark, 2003	Observational case series	Mixed pain conditions ($n=3$) (peripheral neuropathy, multiple sclerosis, lower back pain)	1–9-month observation period	Morphine (75–360 mg daily)	Smoked cannabis plant, unknown content	Mean baseline morphine dose of 195 mg (SD 147 mg) compared with 35 mg (SD 31 mg) after commencing smoked cannabis. Opioid dose reduction or cessation in each case.	Improved pain control described, with patients either reducing or ceasing morphine dose.	GRADE rating 'very low'.

(b) Study reference	Study design	Population	Follow-up period	Opioid used	Cannabinoid used	Effect of cannabinoid on opioid dose	Outcome on analgesia observed	GRADE evidence rating and other notes
Controlled trials								
Johnson *et al*, 2010	Multicenter, double-blind, randomized, placebo-controlled, parallel-group trial.	Patients with cancer pain ($n=177$), with inadequate analgesia despite chronic opioid dosing.	2 weeks	Varied opioids reported as OME (IQR) 120 mg (50–213)	Patients randomized to delta-9-THC : CBD, delta-9-THC, or placebo Delta-9-THC (mean 9 sprays per day)	No change in median amount of breakthrough opioid medication in any group.	Change in pain NRS (out of 10) from baseline was statistically significantly in favor of delta-9-THC : CBD compared with the placebo –1.01 ($p=0.245$)	GRADE rating 'high'. Placebo-controlled and randomized.
				80 mg (30–180)	Delta-9-THC : CBD (mean 10 sprays per day)		–1.37 ($p=0.014$)	
				120 mg (40–240)	Placebo (mean 11 sprays/day)		–0.69 (reference group)	

Table 2 Continued

(b) Study reference	Study design	Population	Follow-up period	Opioid used	Cannabinoid used	Effect of cannabinoid on opioid dose	Outcome on analgesia observed	GRADE evidence rating and other notes
Lissoni *et al*, 2014	Two groups (not randomized): cannabinoid tincture or melatonin	Patients with untreatable metastatic solid tumor ($n=26$)	Not stated	Oxycodone, median dose of 30 mg (10–60 mg), twice per day	Cannabis flos (19% delta-9-THC) was given as an infusion. 100 ml (500 mg/l water) three times per day	5/12 patients (42%) achieved control of pain without opioid dose increase compared to the control group, where 2/14 (14%) achieved pain control	The number that achieved pain control was not significantly different between groups	GRADE rating 'low'. Non-randomized design, no allocation concealment described. Control group received melatonin (20–100 mg). Greater disease progression documented in the cannabis group
Narang *et al*, 2008	Phase 1: randomized, single-dose, double-blinded, placebo-controlled, crossover trial. Primary outcome measures TOTPAR score	Patients on opioids for chronic pain; BPI $\geqslant 4$ ($n=30$). Pain diagnosis: neuropathic ($n=7$), nociceptive ($n=7$), mixed neuropathic and nociceptive ($n=11$), and uncategorized ($n=5$)	Phase 1: three 8-h lab sessions with 3 days washout	OME mean 68.1 mg (SD 57.2, range 7.5–228). Participants were taking oxycodone, morphine, methadone hydrocodone, and hydromorphone	Phase 1: single-dose placebo, dronabinol 10 and 20 mg	One subject took rescue pain medication in all conditions, one subject took rescue medication during the placebo and 10 mg dronabinol condition, and six subjects took rescue medication only with placebo.	In single-dose studies, 10 and 20 mg dronabinol significantly increased the amount of analgesic relief reported compared to placebo	GRADE rating 'moderate'. Randomized and placebo-controlled. Downgraded as only a single dose was examined. TOTPAR 31.1 in placebo group, compared with 39.7 with dronabinol 10 mg and 41.7 with dronabinol 20 mg
	Phase 2: open-label (no placebo) extension. Primary outcome measure change in pain intensity		Phase 2: open label for 4 weeks		Phase 2: flexible dose schedule, dronabinol 5 mg daily – 20 mg three times per day.	Opioid dose not reported	Mean baseline NRS of 6.9 compared with 5.2 after 4 weeks of dronabinol. This represents a statistically significant reduction	GRADE rating 'low'. Open-label study. Significant improvements ($p<0.05$) in sleep, energy, pain relief, and social functioning. Lack of placebo control means effects may be non-specific or placebo
Portenoy *et al*, 2012	Randomized, 4-arm placebo-controlled, graded-dose study	Patients with active cancer and chronic pain on a stable oral morphine regimen, plus fentanyl ($n=360$)	5 weeks of medication administration	Morphine and fentanyl Median 120 mg OME Median 120 mg OME Median 180 mg OME Median 120 mg OME	Nabiximols 1–4 sprays Nabiximols 6–10 sprays Nabiximols 11–16 sprays Placebo	No change in median amount of breakthrough opioid medication in any group. Note that patients were discouraged from reducing their opioid dose, so the opioid-sparing effect could not be observed	Treatment difference (change from baseline pain score): –0.75 points (95% CI–1.28, –0.22, $p=0.06$ compared to placebo) –0.36 points (95% CI –.089, 0.18 points, $p=0.19$ compared to placebo). –0.09 points (95% CI: –0.62, 0.44 points, $p=0.75$ compared to placebo) Not reported (reference group)	GRADE rating 'high'. Placebo-controlled, randomized controlled trial Opioid composite measure showed better improvements in the low-dose group. 1–4 spray group had significant improvements in analgesia. Lower tolerability of delta-9-THC : CBD in higher dose groups
Seeling *et al*, 2006	Randomized, controlled trial (two groups)	Prostate cancer patients <70 y.o. ($n=105$). $N=53$ in intervention and 52 in control	From the day prior to surgery to two days post operation	Piritramide 1.5 mg/ml, bolus 2 mg (no continuous infusion) via patient-controlled analgesia for 48 h post operation	Dronabinol 5 mg × 8 doses over 48 h (perioperatively)	Median dose of piritramide alone was 74 mg (IQR 44–90) compared with 54 mg (IQR 46–88) when administered with dronabinol	The difference between the intervention (dronabinol) group and control group was not significant. No evidence was found of synergistic antinociceptive interaction between delta-9-THC and piritramide for acute postoperative pain	GRADE rating 'high'. Placebo-controlled, randomized controlled trial Patients administered their own opioid doses

Abbreviations: BPI, brief pain inventory; CBD, cannabidiol; GRADE, Grading of Recommendations Assessment, Development and Evaluation; IQR, interquartile range; NRS, numerical rating scale; OME, oral morphine equivalents; TOTPAR, total pain relief.

trials provided high-quality evidence. None of the high-quality studies provided evidence of an opioid-sparing effect. The only study that provided direct evidence of an opioid-sparing effect was rated as providing very low-quality evidence (Lynch and Clark, 2003).

DISCUSSION

Twenty-eight studies provided data relating to the potential opioid-sparing effect of cannabinoids in the context of opioid analgesia. Most of the pre-clinical studies examined reported reduced opioid requirements when co-administered with cannabinoids. Few controlled clinical studies measured opioid-sparing as an end point and findings relating to analgesia were mixed. Two controlled studies found no effect of cannabinoids on opioid dose requirements (Johnson *et al*, 2010; Seeling *et al*, 2006). One case series provided very low-quality evidence of a reduction in opioid dose requirements with cannabinoid co-administration (Lynch and Clark, 2003).

Most of the pre-clinical studies examined found synergistic effects when opioids and cannabinoids were co-administered, although two studies found that with specific opioids and cannabinoids the analgesic effect was additive rather than synergistic. Through meta-analyses, it was found that the doses of morphine and codeine required to produce the same analgesic effect were 3.6 and 9.5 times lower, respectively, when co-administered with delta-9-THC. Reductions in opioid requirements that are smaller than those seen in these pre-clinical studies may have relevance to pain treatment. Some confidence in these findings comes from the consistent observation of an opioid-sparing effect when using different nociceptive assays and in pain models of arthritis and diabetic neuropathy.

The relevance of the findings from these pre-clinical studies (with acute-dosing paradigms) to clinical chronic pain treatment must be considered. There are important limitations in translating findings from pre-clinical studies to clinical practice, particularly when evaluating doses and effect sizes. Although the outcomes of pre-clinical studies are often consistent with clinical studies, pre-clinical studies may over-represent effects. The lesser effect sizes in human studies have been attributed to the heterogeneity of clinical populations or the response being limited to sub-populations, reducing the overall effect observed (Berge, 2011). This underscores the importance of clinical studies to examine the effects found in pre-clinical work.

Controlled clinical studies demonstrated some beneficial effects of opioid and cannabinoid co-administration on outcomes of pain, sleep, and functioning in chronic pain patients (Abrams *et al*, 2011; Narang *et al*, 2008). One case series ($n=3$) provided very low-quality evidence of a reduction in opioid requirements with delta-9-THC administration. No randomized controlled studies were identified that provided evidence of an opioid-sparing effect of cannabinoids. Important limitations identified in these clinical studies included a lack of placebo control (Abrams *et al*, 2011; Lynch and Clark, 2003; Narang *et al*, 2008), difficulties extrapolating from experimental to clinical pain (Naef *et al*, 2003; Roberts *et al*, 2006), use of single doses (Naef *et al*, 2003; Roberts *et al*, 2006), use of small sample sizes (Lissoni *et al*, 2014; Lynch and Clark, 2003; Narang *et al*, 2008), and the mixed quality of the study design in general. In particular, Roberts *et al* (2006) used sub-therapeutic doses of morphine, which may have limited that study's ability to test the effects of co-administration. Portenoy *et al* (2012) noted that the use of fixed dose ranges of cannabinoids may have limited that study's ability to test the efficacy of cannabinoids for pain, as some patients may have dropped out due to tolerability. Moreover, by discouraging patients from reducing their opioid dose during the study, no opioid-sparing effect could be observed (Portenoy *et al*, 2012).

This review highlights some important considerations for future studies of cannabinoids. A dose-ranging study with patients with advanced cancer found that only lower doses of cannabinoids demonstrated analgesic effects (Portenoy *et al*, 2012). In the same study, one in four participants in the high-dose group discontinued treatment. Side effects such as nausea, drowsiness, and dizziness are more frequent with higher doses of cannabinoids (Narang *et al*, 2008; Portenoy *et al*, 2012). This suggests that dose range and tolerability are important outcomes to examine and that careful dose titration is essential. Future studies should carefully document adverse effects from concurrent opioid and cannabinoid administration to provide a better understanding of potential harms. One hypothesis to explain why patients reduce their opioid dose with cannabinoid administration is that they experience undesirable psychoactive effects from concurrent use of opioids and cannabinoids. This could be explored in future studies.

Recent observational studies provided further data on a possible opioid-sparing effect. Two studies found 44–64% reductions in self-reported opioid consumption in cohorts of patients with chronic pain who were using cannabis (Boehnke *et al*, 2016; Haroutounian *et al*, 2016). These observational studies provide further low-quality evidence supporting an opioid-sparing effect. A further observational study found that in patients with chronic pain who were prescribed opioids, greater pain relief was reported from cannabis than from their other medications (Degenhardt *et al*, 2015). A single case study also reported reduced requirements for breakthrough pain with oral delta-9-THC administration (Holdcroft *et al*, 1997). Taken together, these reports support the need for high-quality studies to directly assess the opioid-sparing effect of cannabinoids under controlled conditions.

This review identified some limitations in the literature. The pre-clinical studies examined used a range of animal populations, antinociceptive assays, opioids, and cannabinoids, and often had small numbers of animals per group. This resulted in statistical heterogeneity. Despite this, a large and significant effect was observed in the meta-analysis. No studies examined the opioid-sparing effect of cannabidiol alone, in combination with delta-9-THC outside of a 1 : 1 ratio, or with other cannabinoids. Further, the lack of high-quality studies in humans investigating the opioid-sparing effect means that the evidence for this is largely limited to pre-clinical studies. A funnel plot was produced and did not provide evidence of publication or small study bias; however, due to the small number of studies in the meta-analysis (<10) the interpretation of the funnel plot is limited.

The potential for cannabinoids to reduce opioid dose requirements and extend the duration of effective analgesia should not be understated. The rapid increase in opioid use and opioid-associated mortality is largely attributed use of opioids in chronic pain treatment (Chou *et al*, 2015; Zedler *et al*, 2014). Use of lower opioid doses has been recommended (Dowell *et al*, 2016); however, clinical processes to achieve this reduction are not well defined. Opioid-sparing medications may have enormous clinical relevance by enabling effective pain treatment with lower opioid doses and a potential reduction in opioid-related mortality.

In conclusion, pre-clinical studies support the opioid-sparing effect of delta-9-THC. However, the findings from clinical trials are inconsistent, with some studies found to have important limitations such as a lack of placebo control. An opioid-sparing effect of cannabinoids in chronic pain patients was observed in only one very-low-quality clinical study. These findings provide an early signal that warrants exploration. It remains to be seen if these promising pre-clinical and observational findings can be replicated in large, well-designed clinical studies.

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Supplementary Information accompanies the paper on the *Neuropsychopharmacology* website (http://www.nature.com/npp)