Critique author	**Ed Whitney**

Bibliographic Data	
Authors	Whiting PF, Wolff RF, et al
Title	Cannabinoids for Medical Use: A Systematic Review and Meta-analysis
PMID	26103030
Citation	JAMA 2015;313(24):2456-2473.
Other information if relevant	The article covers multiple medical applications of cannabinoids, including chronic pain, nausea and vomiting due to chemotherapy, appetite stimulation in HIV/AIDS, spasticity due to MS or paraplegia, depression, anxiety, sleep disorder, glaucoma, psychosis, and movement disorders due to Tourette syndrome

Methods	
Aim of study	To review the benefits and adverse effects of cannabinoids for medical use
Design	Systematic review and meta-analysis of randomized clinical trials

PICOS	**For chronic pain only**
Population from which participants are drawn	Patients with chronic pain, neuropathic pain, and cancer pain
Intervention being evaluated	Smoked THC Nabixomols
Comparison or control intervention	Placebo, usual care, no treatment
Outcomes	Pain reduction 30% NRS or VAS scores Brief Pain Inventory Patient global impression of change

Study types	Randomized clinical trials only

Study selection	
Search date of literature review	April 2015
Databases in literature search	28 databases were searched, including MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews, the Allied and Complementary Medicine Database, Web of Knowledge, and others
How authors assessed study quality (risk of bias and other considerations	The Cochrane Risk of Bias tool, with ratings for randomization method, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and "other biases" If one of the Cochrane items had a high risk of bias, the entire study was considered to be at a high risk of bias; only if all items were considered to be low risk of bias was the study classified as low risk of bias; all other studies were classified as unclear risk of bias
Additional information if relevant	

Results	
Number of studies screened	505 full reports were assessed for all medical conditions evaluated in the meta-analysis
Number of studies selected for analysis of results	- For Chronic Pain, 28 studies with 63 reports were included - 13 studies evaluated nabiximols, 4 evaluated smoked THC, 5 evaluated nabilone, 3 evaluated THC oral spray, 1 evaluated vaporized cannabis, 1 evaluated ajuvenic acid capsules, and 1 evaluated oral THC
Whether authors elected to perform meta-analysis to pool study results statistically and type of meta-analysis done (fixed effect or random effects, heterogeneity, etc)	For the outcome of 30% pain reduction , a random effects model was used; other pain outcomes were not subjected to meta-analysis due to inadequate data for pooling of effect sizes
Quality of studies as assessed by authors	Only two of the 28 studies were rated at a low risk of bias; 9 were at unclear risk, and 17 were at a high risk of bias

Effect sizes reported for primary outcomes (mean differences, standardized mean differences, response ratios, etc)	- The authors displayed a forest plot for eight studies where the outcome was a 30% pain reduction - Seven of these studies were of nabiximols; one was of smoked cannabis - Four of these studies were at high risk of bias and four were at unclear risk of bias - Two of the studies were of cancer pain, and six were of neuropathic pain, either due to diabetes, HIV, or central pain - The pooled odds ratio for 30% pain reduction from the eight studies was 1.41 with a 95% confidence interval 0.99-2.00 - The odds ratios for neuropathic pain and for cancer pain were not significantly different from one another
Effect sizes reported for additional outcomes (mean differences, standardized mean differences, response ratios, etc)	- Six studies reported the average reduction on the Numerical Rating Scale (NRS) for pain - The pooled effect size for NRS reduction was 0.45 points on a 10 point scale, 95% CI 0.11-0.80 - There were no differences between nabiximols and placebo on average quality-of-life scores as measured in three trials
Additional information if relevant	- Sleep disorder was briefly addressed, and cannabinoids (mainly nabiximols) were associated with improvements in sleep quality and sleep disturbance, but the magnitude of the improvements is not clear - Adverse events were reported in 62 studies, and an analysis of the data did not show that the risk of an adverse event depended on the type of cannabinoid - For the category of “serious” adverse events, data from 34 studies (3248 patients) had an odds ratio of 1.41 (95% CI was 1.04 to 1.92) - Several specific adverse events had significant odds ratios for cannabinoids versus placebo: dizziness (5.09), dry mouth (3.50), nausea (2.08), fatigue (2.00), somnolence (2.83), euphoria (4.08), disorientation (5.41), drowsiness (3.68), confusion (4.03), asthenia (2.03), balance problems (2.62), hallucination (2.19), vomiting (1.67)

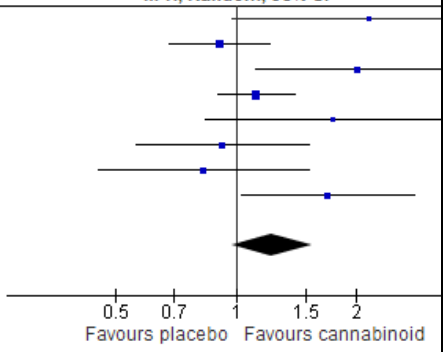
Conclusions	
Key conclusions of study authors	- There was moderate quality evidence to suggest that cannabinoids (smoked THC or nabiximols) may be beneficial for the treatment of neuropathic pain or cancer pain - Only two studies evaluated cannabis, but there is no evidence that the effects of cannabis differed from those of other cannabinoids - Many short-term adverse events were associated with cannabinoids, but no studies of long-term adverse events were identified - Most studies were of low quality and at unknown or high risk of bias
Additional information if relevant	

Comments by DOWC staff

- The overall quality of the study data for chronic pain, due to the high risk of bias in four of the studies and unclear risk of bias in the other four studies, probably falls short of Division standards for "good" evidence, but the authors do not provide information regarding which Risk of Bias criteria were considered deficient in the included studies
- The two pain studies considered to be "low risk of bias" were not included in the pooled summary of 30% pain reduction, presumably because they did not report that outcome
- Figure 2, which displays the forest plot for "Improvement in Pain" for cannabinoids versus placebo, gives the odds ratio of 1.41 for a 30% reduction in pain
- Because the odds ratio inflates the "relative risk" of an outcome when that outcome occurs frequently in a population, it is important to note that the data can be reanalyzed to calculate a "response ratio" for that favorable outcome, and it is only 1.23 with a 95% CI 0.98 to 1.56:

	Cannabinoid		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Abrams 2007	13	25	6	25	6.6%	2.17 [0.98, 4.79]	
GW 2005	54	149	59	148	19.5%	0.91 [0.68, 1.22]	
Johnson 2010	23	53	12	56	10.1%	2.03 [1.12, 3.65]	
Langford 2013	84	167	77	172	22.3%	1.12 [0.90, 1.41]	
Nurmikko 2007	16	63	9	62	7.4%	1.75 [0.84, 3.66]	
Portenoy 2012	22	90	24	91	12.3%	0.93 [0.56, 1.53]	
Selvarahah 2010	8	15	9	14	9.6%	0.83 [0.45, 1.53]	
Serpell 2014	34	123	19	117	12.2%	1.70 [1.03, 2.81]	
Total (95% CI)		**685**		**685**	**100.0%**	**1.23 [0.98, 1.56]**	
Total events	254		215				

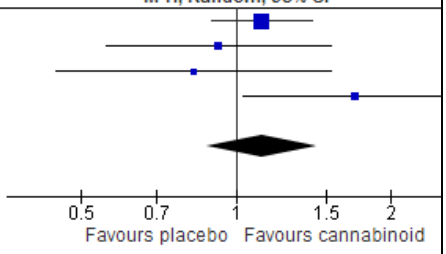
Heterogeneity: Tau² = 0.05; Chi² = 14.15, df = 7 (P = 0.05); I² = 51%
Test for overall effect: Z = 1.75 (P = 0.08)



- If the four "high risk of bias" studies (Abrams 2007, GW Pharmaceuticals 2005, Johnson 2010, and Nurmikko 2007) are removed from the analysis, the four remaining "uncertain risk of bias" studies have a pooled response ratio of only 1.12 with 95% CI 0.88 to 1.44:

	Cannabinoid		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Langford 2013	84	167	77	172	48.9%	1.12 [0.90, 1.41]	
Portenoy 2012	22	90	24	91	18.8%	0.93 [0.56, 1.53]	
Selvarahah 2010	8	15	9	14	13.5%	0.83 [0.45, 1.53]	
Serpell 2014	34	123	19	117	18.7%	1.70 [1.03, 2.81]	
Total (95% CI)		**395**		**394**	**100.0%**	**1.12 [0.88, 1.44]**	
Total events	148		129				

Heterogeneity: Tau² = 0.02; Chi² = 4.21, df = 3 (P = 0.24); I² = 29%
Test for overall effect: Z = 0.93 (P = 0.35)



- One of these "low risk of bias" trials, Wilsey 2013, did measure 30% pain reduction as an outcome, but it could not be combined with the studies in Figure 2 because it was a crossover trial and not a parallel group trial
- Wilsey had the same patients with neuropathic pain use three different preparations of vaporized cannabis in random order: medium dose (3.53% THC), low dose (1.29% THC), and placebo
- Wilsey reported no difference in 30% pain reduction between medium and low dose THC, but found that both doses of THC were more effective than placebo in attaining a 30% pain reduction

Comments by DOWC staff continued

- The other "low risk of bias" trial, Ware 2010, also used a crossover design with four dose levels of smoked cannabis: 9.4%, 6%, 2.5%, and placebo, but reported VAS scores rather than 30% pain reduction responses, and the primary outcome was a comparison of VAS scores with 9.4% versus 0% cannabis
- Ware reported a difference of mean VAS between the 9.4% THC (5.4) versus 0% THC (6.1), with a mean difference of 0.7 points, a clinically small effect size
- A consistent moderate effect with these two higher quality studies, combined with the lower quality results from the studies in Figure 2, warrants a "good" evidence statement that cannabinoids containing THC are associated with a small to moderate improvement in chronic pain as compared to placebo
- Even if the success rates from the eight pooled trials represent an unbiased estimate of the population success rates for cannabinoids, the absolute success rate is 254 successes out of 685 treated patients, which equals 37% of treated patients responding with a 30% pain reduction, versus a 31% success rate with placebo (the rate of 37% is unchanged by removal of the studies with a high risk of bias)
- A 37% success rate is very modest in size, and is approximately in line with other commonly used analgesics for chronic pain

Assessment by DOWC staff	
Overall assessment as suitability of evidence for the guideline ☒ High quality ☐ Adequate ☐ Inadequate	There is good evidence that cannabinoids containing THC are associated with a small to moderate improvement in chronic pain compared to placebo; however, the dosage needed to produce an analgesic effect is undefined and uncertain
If inadequate, main reasons for recommending that the article not be cited as evidence	- The support for evidence favoring cannabinoids is justified by the two crossover studies with low risk of bias which were included in the systematic review but not included in the pooled effect estimate of the meta-analysis

Additional references if relevant

- Wilsey B, Marcotte T, et al. Low-dose vaporized cannabis significantly improves neuropathic pain. J Pain 2013;14(2):136-148.
- Ware MA, Wang T, et al. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. CMAJ 2010;182(14):E694-701