Critique author	Ed Whitney

Bibliographic Data	
Authors	Abdel Shaheed CA, Maher CG, et al
Title	Efficacy, tolerability, and dose-dependent effects of opioid analgesics for low back pain: a systematic review and meta-analysis.
PMID	27213267
Citation	JAMA Intern Med. doi:10.1001/jamainternmed.2016.1251.
Other information if relevant	

Methods	
Aim of study	To evaluate the efficacy and tolerability of opioids in the management of back pain
Design	Systematic review and meta-analysis

PICOS	
Population from which participants are drawn	Patients with nonspecific low back pain where a cause (fracture, infection, etc) had not been identified
Intervention being evaluated	Single-ingredient or combination medicines containing an opioid analgesic
Comparison or control intervention	Placebos Other drugs of the same class Different doses of the same drug
Outcomes	Short-term pain relief (followup <3 months) Intermediate-term relief (between 3 and 12 months) Long-term relief (>12 months) Disability Adverse event outcomes

Study types	Randomized clinical trials Trials including a variety of pain conditions were eligible for inclusion provided that low back pain patients were reported separately and could be separately analyzed

Study selection	
Search date of literature review	Through September 2015
Databases in literature search	MEDLINE, EMBASE, CENTRAL, CINAHL, the Cochrane Database of Systematic Reviews, and PsycINFO
How authors assessed study quality (risk of bias and other considerations	- 2 authors independently assessed articles for inclusion in the review and independently rated them for risk of bias using the 11-item PEDro scale - A PEDro score of 7 or more out of 10 was considered to be at a low risk of bias; scores less than 7 were considered at a high risk of bias - Overall quality of evidence for a recommendation was rated using GRADE criteria, which can downgrade the quality of evidence for 4 factors: poor study design (>25% of trials had a PEDro score <7), inconsistency of results (>25% of trials had results not in the same direction), imprecision (sample size <300), and publication bias - Quality of evidence was defined as high quality, moderate quality, low quality, and very low quality
Additional information if relevant	- Study selection stipulated that the patients be stabilized on the medication of interest and the pattern of use was not changed during the study - All opioid doses were converted to morphine equivalent doses for purposes of analysis - Pain scores were all converted to a scale from 0 (no pain) to 100 (maximum pain) in order to allow the combined results to estimate mean differences between opioids and the comparison treatments

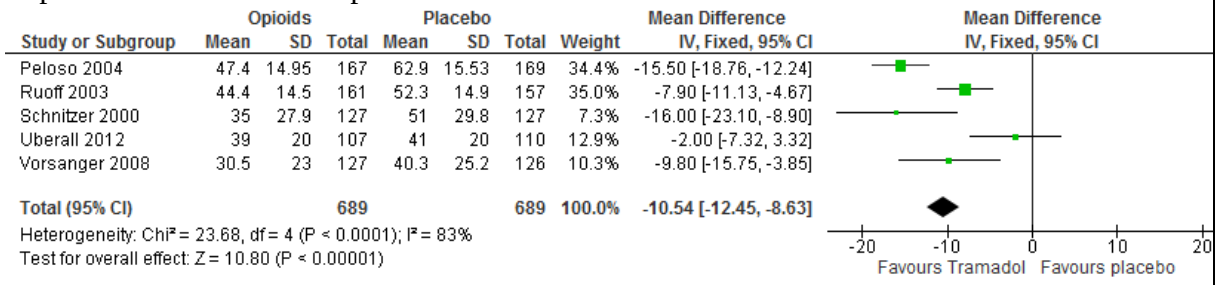
Results	
Number of studies screened	- 13.094 study titles were screened for eligibility - 195 articles were identified for abstract review
Number of studies selected for analysis of results	- 20 studies were included for the final analysis - 19 of these studied patients with chronic LBP, and 1 studied subacute LBP

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)	- Where possible, meta-analysis pooled results using a random-effects model - Possible sources of heterogeneity were explored when I^2 was >40% - In addition, the authors explored whether the study design (enriched enrollment versus non-enriched enrollment) had an influence on the estimate of drug efficacy
Quality of studies as assessed by authors	- There was moderate quality evidence from 13 studies regarding single-ingredient opioids for short term pain relief - There was high-quality evidence from 6 studies regarding single-ingredient opioids intermediate term pain relief - There was very low-quality evidence from single studies regarding intermediate and short-term disability related to chronic LPB
Effect sizes reported for primary outcomes (mean differences, standardized mean differences, response ratios, etc)	- The mean difference for the 13 short-term pain relief studies was 10.1 points for opioids being superior to placebo (95% CI 7.4 to 12.8 points) - The mean difference for the 6 intermediate-term pain relief studies was 8.1 points for opioids being superior to placebo (95% CI 6.0 to 10.2 points)
Effect sizes reported for additional outcomes (mean differences, standardized mean differences, response ratios, etc)	- For improvements in disability, the available (low quality) studies did not show a significant effect of opioids in the short or in the intermediate term - Half of the trials had 50% of the patients drop out because of adverse events or lack of efficacy - Studies rarely reported the severity or duration of adverse events - The median rates for adverse events in the randomized phase of the trials was 49.1% for placebo and 68.9% for opioids - Common adverse events were headache, somnolence, dizziness, gastrointestinal adverse events, and autonomic effects such as dry mouth - Over half of the patients who experienced an adverse event completed the studies in which they were enrolled
Additional information if relevant	- The pooled effect sizes for opioids were approximately half of the 20 point threshold for clinical importance on a 100 point scale - The effect of study design did not appear important; the results from enriched and non-enriched enrollment designs were approximately equal - There were clinically unimportant differences (7.6 points or less) between drugs in head-to head comparisons of different strengths of the buprenorphine patch (20 mcg/hr versus 5 mcg/hr) and oxycodone vs the buprenorphine patch

Conclusions	
Key conclusions of study authors	- Opioid analgesics relieve pain in the short and intermediate term in the setting of chronic low back pain - These analgesic effects are small and are about half the threshold for clinical importance - However, these are group mean differences, and some individuals may gain meaningful pain relief from opioids while others receive no benefit - It is doubtful that opioids improve disability - Adverse events are common with opioids, and many trial patient stop taking the drug because of side effects or lack of efficacy - An enrichment design does not appear to influence estimates of treatment efficacy
Additional information if relevant	

Comments by DOWC staff

- Because it appears that most published studies of opioid efficacy do not report group differences in terms of responders (percent of patients with 33% or 50% pain relief), the meta-analysis was constrained to report comparisons of mean
- The short and intermediate term pain relief reported in the included studies is likely to represent an optimistic estimate of their effectiveness if continued for months or years
- The authors acknowledge that some individuals may benefit from opioids, but at this time there is no guidance as to how to identify these individuals
- A dose-response analysis was done using log-transformed opioid doses in terms of morphine equivalent doses, which were originally designed to provide guidance for opioid switching when managing patients, and are being used here outside their validated domain
- A recent Cochrane review (Chaparro et al 2013) of the same topic included most of the same studies but appeared to come to a slightly different conclusion: that there was some evidence for short-term efficacy for opioids in chronic nonspecific low back pain
- For example, Chaparro's Analysis 1.1 compared tramadol versus placebo for short-term pain intensity, and estimated a standardized mean difference (SMF) of 0.55 SD in favor of tramadol, which is conventionally considered to be a moderate treatment effect (a SMD between 0.5 and 0.8 is rated as "moderate")
- Chaparro pooled pain intensity with the original pain scores, some of which were on a scale of 0-10 and some of which were on a scale of 0-100; because these are different scales of measurement, it is necessary to pool them using standard deviation differences as measures of efficacy
- Abdel Shaheed transformed all pain scores to a scale of 0-100 and reported treatment effects in terms of mean differences between opioid and placebo
- It is possible to re-analyze Chaparro's Analysis 1.1 in mean differences by the same methods used by Abdel Shaheed; the SMD is the same but the mean difference is 10.54, which is consistent with Abdel Shaheed's conclusion that the mean difference is half of the clinically important difference of 20 points



Study or Subgroup	Opioids Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Peloso 2004	47.4	14.95	167	62.9	15.53	169	34.4%	-15.50 [-18.76, -12.24]
Ruoff 2003	44.4	14.5	161	52.3	14.9	157	35.0%	-7.90 [-11.13, -4.67]
Schnitzer 2000	35	27.9	127	51	29.8	127	7.3%	-16.00 [-23.10, -8.90]
Uberall 2012	39	20	107	41	20	110	12.9%	-2.00 [-7.32, 3.32]
Vorsanger 2008	30.5	23	127	40.3	25.2	126	10.3%	-9.80 [-15.75, -3.85]
Total (95% CI)			**689**			**689**	**100.0%**	**-10.54 [-12.45, -8.63]**

Heterogeneity: Chi² = 23.68, df = 4 (P < 0.0001); I² = 83%
Test for overall effect: Z = 10.80 (P < 0.00001)

- Therefore, the discrepancy between Abdel Shaheed may be more apparent than real; the moderate sized SMD from Chaparro is attributable to the variances in pain scores rather than clinically important differences

Assessment by DOWC staff	

Overall assessment as suitability of evidence for the guideline x☐ High quality ☐ Adequate ☐ Inadequate	High quality meta-analysis providing strong evidence that in the setting of chronic nonspecific low back pain, the short and intermediate term reduction in pain intensity of opioids, compared with placebo, falls short of a clinically important level of effectiveness There is strong evidence that adverse events such as constipation, dizziness, and drowsiness are more frequent with opioids than with placebo There is an absence of evidence that opioids have any beneficial effects on function or reduction of disability in the setting of chronic nonspecific low back pain
If inadequate, main reasons for recommending that the article not be cited as evidence	

Additional references if relevant
- Chaparro LE, Furlan AD, et al. Opioids compared to placebo or other treatments for chronic low-back pain. Cochrane Database of Systematic Reviews 2013, Issue 8. Art. No.: CD004959