Critique author	**Ed Whitney**

Bibliographic Data	
Authors	Wolff RF, Aune D, et al
Title	Systematic review of efficacy and safety of buprenorphine versus fentanyl or morphine in patients with chronic moderate to severe pain.
PMID	22443154
Citation	Curr Med Res Opin. 2012 May;28(5);833-45.
Other information if relevant	

Methods	
Aim of study	To compare the safety and efficacy of buprenorphine patches versus fentanyl patches in the setting of chronic moderate to severe pain
Design	Network meta-analysis of randomized clinical trials

PICOS	
Population from which participants are drawn	Adults over 18 diagnosed with chronic moderate to severe pain due to any cause
Intervention being evaluated	Buprenorphine patch
Comparison or control intervention	Fentanyl patch

Outcomes	- Any measurement of pain intensity, pain relief, Patient Global Impression of Change (PGIC), or responder rates - Symptoms such as fatigue, anxiety, etc - Dose increases - Antihyperalgesic effects - Treatment discontinuation due to lack of effect - Sleep quality - Quality of life (QOL) - Serious adverse effects which require hospitalization or are life-threatening - Adverse events not requiring hospitalization - Morbidity and mortality rates - Respiratory depression - Treatment discontinuation due to adverse effects
Study types	- Parallel randomized clinical trials - Crossover trials, provided that data from the first period were reported separately

Study selection	
Search date of literature review	Up through December 2010
Databases in literature search	MEDLINE, EMBASE, LILACS, DARE, PsychINFO, Cochrane Central Register of Controlled Trials and websites such as the FDA and others
How authors assessed study quality (risk of bias and other considerations	Using the Cochrane Risk of Bias Tool - Generation of randomization sequence - Allocation concealment - Maintenance of blinding throughout the study - Incomplete outcome data adequately addressed - Freedom from selective outcome reporting - Freedom from other biases
Additional information if relevant	

Results	

Number of studies screened	430 articles were selected for full text screening
Number of studies selected for analysis of results	46 studies were selected for analysis 14 of these were efficacy analyses, and 32 were safety/adverse event analyses, and there were more than 2600 patients in the 14 efficacy studies
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)	- There were no direct comparisons of fentanyl versus buprenorphine - Consequently, the authors undertook a network meta-analysis, in which fentanyl and buprenorphine were compared indirectly through common comparisons with either placebo or morphine - That is, there were 4 studies comparing buprenorphine with placebo, and 2 studies comparing fentanyl with placebo; in this instance, the effect sizes of buprenorphine versus placebo were compared with the effect sizes of fentanyl versus placebo, and the effect size of buprenorphine versus fentanyl was estimated indirectly - Similarly, there was one study comparing buprenorphine with morphine, and 7 studies comparing fentanyl versus morphine, and again, the comparison of buprenorphine versus fentanyl was made indirectly - 6 enriched and 8 non-enriched enrollment studies were included in the review - The authors carried out one analysis for the 8 non-enriched studies and a separate analysis for all 14 studies combined
Quality of studies as assessed by authors	- There were six criteria upon which the risk of bias was estimated, and no study received more than 3 “yeses” - Most studies were rated as “unclear” on the generation of the randomization sequence and on allocation concealment

Effect sizes reported for primary outcomes (mean differences, standardized mean differences, response ratios, etc)	- The pooled results for the 8 non-enriched clinical trials were done first, and are summarized below: - For all included pain measures, fentanyl and buprenorphine did not differ from one another - However, there were elevated odds ratios (OR) for some comparisons of adverse effects, in which fentanyl had more adverse events than buprenorphine - For nausea, the OR was 4.66 with a 95% confidence interval 1.07 to 20.39 - For discontinuations due to adverse events, the OR was 5.94 with a 95% CI 1.78 to 19.87 - Fentanyl and buprenorphine had similar outcomes for sleep quality, constipation, and discontinuation due to lack of effect - Compared to morphine, buprenorphine had a significantly greater effect on pain intensity on a 100 point scale (16.20 points, 95% CI 3.48 to 28.92) - Morphine produced more constipation (OR=7.50) and discontinuations due to adverse events (OR=5.80) than buprenorphine - Morphine and buprenorphine had similar rates of adverse events such as nausea and discontinuation due to lack of effect, and effects on sleep quality were similar - In comparison with buprenorphine, placebo had higher rates of discontinuation due to lack of effect (OR=2.36), but there were non-significant differences between buprenorphine and placebo for pain intensity, constipation, nausea, and treatment discontinuation due to adverse effects
Effect sizes reported for additional outcomes (mean differences, standardized mean differences, response ratios, etc)	- One additional analysis (reported in Table 3 but not in the text) showed no difference between placebo and morphine with respect to pain intensity, either in the 4 non-enriched studies nor in the 5 enriched studies which were available for analysis - There were no head-to-head comparisons of placebo versus morphine for the above comparison; the network analyses were inferred from studies of morphine versus buprenorphine and of morphine versus fentanyl - In Table 5, both fentanyl and buprenorphine appear to cause less constipation than morphine - That is, the odds ratio for constipation of morphine versus buprenorphine is 7.50, and the odds ratio for morphine versus fentanyl is 1.76
Additional information if relevant	Analyses which combined all 14 studies, enriched and non-enriched, yielded estimates of treatment effect which were similar to the estimates from the non-enriched analyses alone

Conclusions	
Key conclusions of study authors	- Comparisons between fentanyl and buprenorphine had to be done through adjusted indirect comparison, since there were no head-to-head comparisons of the two transdermal medications - This means that the findings are subject to limitations and uncertainties beyond the control of the authors - The quality of the included studies is a further limitation of the meta-analysis, since none of the studies met more than three of the six quality criteria for control of bias - Nevertheless, it is likely that buprenorphine causes fewer side effects such as nausea and treatment discontinuation due to adverse effects than does fentanyl - With respect to quality of sleep, constipation, and dizziness, there appear to be no differences between buprenorphine and fentanyl - Both buprenorphine and fentanyl are likely to cause less constipation than oral morphine
Additional information if relevant	- Another limitation is the lack of data for long term followup; most of the durations were relatively short, 7 days to 2 months, which is insufficient to detect the long term effects of either buprenorphine or fentanyl

Comments by DOWC staff

- The majority of the included studies enrolled patients with cancer pain, which could account for the lack of long-term followup data which the authors cite as a limitation of the analysis
- The authors based their comparisons between buprenorphine and fentanyl on the 14 enriched and non-enriched randomized trials, including the comparisons for adverse events, as seen in Tables 5 and 6
- However, Figure 1 shows that in addition to the 14 efficacy studies, the authors had 32 studies for adverse events, safety, and tolerability, which were not included in the adverse events tables
- The authors used methods of network meta-analysis which are generally accepted (Song 2009), and probably avoided serious errors in combining studies
- However, Song 2009 discusses two issues concerning indirect comparisons which were not explicitly addressed in the discussion section: that the combined studies be sufficiently homogeneous to allow for pooling of the data, and that a "similarity assumption" be met
- The assumption of homogeneity was not explicitly reported upon, but it is likely that the combined trials met this assumption, which does *not* assume that a fixed effect model has to be justified, only that a pooled analysis be feasible
- The "similarity assumption" assumes that the sets of placebo trials (i.e., buprenorphine versus placebo and fentanyl versus placebo) are sufficiently similar for moderators of relative treatment effects; this may be violated if, for example, some placebo controlled trials enroll patients with very severe pain and other placebo controlled trials enroll patients with moderate or even mild pain
- It is not clear that the similarity assumption was met, and there is one comparison from the meta-analysis which suggests that it was probably violated
- That comparison was in Table 3, where morphine is compared with placebo for pain intensity, and morphine is no different from placebo
- Most of the trials enrolled cancer patients, where morphine is known to be superior to placebo, especially in the relatively short term followup which most trials had
- It is therefore more likely that the indirect comparison of morphine versus placebo was compromised by one of the factors which the authors noted as limitations of the overall meta-analysis
- However, it is likely that the comparisons of adverse effects between buprenorphine and fentanyl are valid, since the odds ratios for nausea (4.66) and discontinuation due to adverse events (5.94) are fairly high, and probably not entirely confounded by the limitations in the data
- It is likely that the comparison of the adverse events from buprenorphine and fentanyl which were derived from mostly cancer studies can be applied to noncancer pain

Assessment by DOWC staff	

Overall assessment as suitability of evidence for the guideline ☐ High quality ☒ Adequate ☐ Inadequate	Adequate meta-analysis supporting good evidence that transdermal fentanyl and transdermal buprenorphine are similar with respect to analgesia and sleep quality, and are similar with respect to some common adverse effects such as constipation and discontinuation due to lack of effect. However, buprenorphine probably causes significantly less nausea than fentanyl, and probably carries a lower risk of treatment discontinuation due to adverse events. It is also likely that both transdermal medications cause less constipation than oral morphine.
If inadequate, main reasons for recommending that the article not be cited as evidence	

Additional references if relevant
- Song F, Loke YK, et al. Methodological problems in the use of indirect comparisons for evaluating healthcare interventions: a survey of published systematic reviews. BMJ 2009;338:b1147.