Critique author	**Ed Whitney**

Bibliographic Data	
Authors	Mattick RP, Breen C, et al.
Title	Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence.
PMID	24500948
Citation	Cochrane Database of Systematic Reviews 2014, Issue 2. Art. No.: CD002207.
Other information if relevant	

Methods	
Aim of study	To compare buprenorphine with placebo and methadone in the management of opioid dependency
Design	Meta-analysis of randomized clinical trials

PICOS	
Population from which participants are drawn	Individuals, other than pregnant women, who are dependent on heroin and other opioids
Intervention being evaluated	Buprenorphine maintenance therapy (BMT) using daily doses above 1 mg using either sublingual tablets or using implants containing buprenorphine
Comparison or control intervention	- Methadone maintenance therapy (MMT) with doses of 20 mg per day or higher - Placebo - Maintenance therapy with buprenorphine at a dose of 1 mg per day

Outcomes	- Retention in treatment over a period of time - Use of opioids as measured by urinalysis positive for heroin or self-reported use of heroin - Use of other substances, such as cocaine and benzodiazepines, as measured by urinalysis - Criminal activity as measured by self-report - Mortality - Physical and psychological health - Adverse effects of medication
Study types	Randomized controlled trials
Additional information if relevant	The number of positive urines, one of the principal outcome measures, were derived from correspondence with the authors of the separate studies, and the data reported in the analyses are not to be found in the published studies themselves

Study selection	
Search date of literature review	January 2003 through January 2013
Databases in literature search	Cochrane Central Register of Controlled Trials, EMBASE, PsycLIT, and several databases which index selected drug and alcohol journals not indexed in main databases
How authors assessed study quality (risk of bias and other considerations	Cochrane Risk of Bias tool for - Random sequence generation - Allocation concealment - Blinding of participants and personnel delivering care - Blinding of outcome assessment - Incomplete outcome data (attrition and withdrawal from study) - Selective outcome reporting

Additional information if relevant	- 11 studies used flexible dosing, and the remainder used fixed dosing - The authors considered flexible dosing studies to be more relevant to real world practice, but reported separately on the fixed and flexible dose studies - Fixed dose studies were classified as low dose, medium dose, or high dose, depending on the number of milligrams of each drug as a daily dose - Low dose was up to 40 mg of methadone and between 2 mg and 6 mg of buprenorphine - Medium dose was 40 mg to 85 mg of methadone and 7 mg to 15 mg of buprenorphine - High dose was over 85 mg of methadone and 16 mg of buprenorphine

Results	
Number of studies screened	1479 records were screened
Number of studies selected for analysis of results	31 studies with 5430 participants were selected for meta-analysis 20 studies compared buprenorphine with methadone 11 studies compared buprenorphine with placebo (placebo could be either true placebo or buprenorphine at a dose of 1 mg/d)
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)	- All of the meta-analyses used random effects models to pool the data - Retention in treatment was assessed as a risk ratio, and the number of positive urines in a study was treated as a continuous variable, where treatment effects were analyzed as standardized mean differences
Quality of studies as assessed by authors	- Although only 22 studies were conducted under double-blind conditions, all studies, including the open-label studies, were considered to be at low risk of bias for assessment of objective outcomes - The studies which were done blinded gave the participants either an active or a placebo methadone syrup and either an active or placebo sublingual buprenorphine preparatoin - Only 13 studies were considered to have adequate random sequence generation, and only 11 were considered to have adequate description of allocation concealment

Effect sizes reported for primary outcomes (mean differences, standardized mean differences, response ratios, etc)	- There were 11 studies with 1391 participants comparing flexible dose buprenorphine with flexible dose methadone - 5 of these studies, with 788 participants, were double-blind - These five double-blind studies indicated that there was a lower rate of retention with buprenorphine (52%) than with methadone (62%), for a retention ratio of 0.83 and a 95% confidence interval 0.72 to 0.95 - The six open-label flexible dose studies had very similar results, again showing lower retention in treatment with buprenorphine (53%) than with methadone (64%, for an RR of 0.80, 95% CI 0.63 to 1.02) - For fixed dose studies, there were 3 studies of low dose buprenorphine versus low dose methadone; buprenorphine was less successful retaining patients in treatment(44%) than methadone (65%) - For fixed dose studies, there were 7 studies of medium dose buprenorphine versus medium dose methadone; buprenorphine was statistically similar to methadone (39% versus 48%) - There was one study of high dose buprenorphine versus high dose methadone; both had very poor retention rates: 5% for buprenorphine and 6.6% for methadone
Effect sizes reported for additional outcomes (mean differences, standardized mean differences, response ratios, etc)	- Rates of positive heroin urines were similar between buprenorphine and methadone, for both fixed and flexible dose studies - Rates of positive cocaine and benzodiazepine urines was also similar between buprenorphine and methadone for both fixed and flexible dose studies - No difference was found with respect to criminal activity between buprenorphine and methadone maintenance - Ten studies reported data on adverse events, but there did not appear to be a systematic difference between buprenorphine and methadone; however, one study reported more sedation with methadone than with buprenorphine
Additional information if relevant	- High dose buprenorphine was superior to placebo with respect to retention in treatment (65.6% vs. 39.7) - High dose buprenorphine was also superior to placebo with respect to morphine-positive urines, but this was not true of low dose and medium dose buprenorphine

Conclusions	
Key conclusions of study authors	- Methadone is better than buprenorphine in retaining opiate dependent patients in treatment over a period of time - Methadone and buprenorphine appear to be equally effective in reducing the use of heroin, as evidenced by urine and self-report - There appears to be no difference between methadone and buprenorphine with respect to use of cocaine and benzodiazepines - Buprenorphine is superior to placebo with respect to retention in treatment, and high dose buprenorphine (16mg/d) is superior to placebo with respect to heroin-positive urines - Buprenorphine could be an alternative to methadone in settings where methadone is not tolerated, when methadone dosing cannot be increased, and perhaps in some settings where alternate day dosing us clinically useful compared to methadone
Additional information if relevant	- It is possible that some of the difficulties associated with buprenorphine retaining patients in treatment is related to the methods of induction, which may have been too slow compared to induction with methadone

Comments by DOWC staff

- The six open label trials comparing buprenorphine with methadone used sublingual buprenorphine, but the five double blind trials used different formulations of buprenorphine: one was not known, one was sublingual, one used a tablet, and two used buprenorphine solutions; both of the latter studies were published in 1994, and did not show a difference in retention rates between buprenorphine and methadone
- Although the meta-analysis of treatment retention did show that buprenorphine had lower dropout rates than methadone, the effect size is fairly modest; the data for all 11 trials had 52.6% retention for buprenorphine and 62.9% for methadone
- Buprenorphine was superior to placebo for retaining patients in treatment, but this does not facilitate decisions regarding referral to methadone vs. buprenorphine
- The data on positive urines appear to support the approximate equivalence of buprenorphine and methadone, but may; be difficult to interpret, since the data had to be furnished through correspondence with the authors of the clinical trials, and was not presented in the published journals
- None of the 11 trials reported that buprenorphine was clearly superior to methadone for retention in treatment or in suppression of heroin use
- Only two studies involved chronic pain patients whose opioid addiction was iatrogenic, and both of these studies were excluded from the analyses
- Although the "Characteristics of included studies" section describes many study participants as having opioid dependence, it appears that the majority of all studies focused on patients referred for heroin dependence
- One new study (Hser 2015) randomized 1080 opioid dependent patients (both prescription and heroin) to buprenorphine or methadone, and followed them for an average of 4.5 years
- Hser reported that opioid use at followup was greater with buprenorphine (42.8%) than with methadone (31.7%) as determined by positive urines; the published data cannot be combined with the data from the current meta-analysis because of differences in ascertainment, but patient participation with buprenorphine treatment appeared to be less than for methadone treatment

Assessment by DOWC staff	
Overall assessment as suitability of evidence for the guideline ☒ High quality ☐ Adequate ☐ Inadequate	High quality meta-analysis supporting strong evidence that in patients being treated with opioid agonists for heroin addiction, methadone is more successful at retaining patients in treatment than is buprenorphine. The rates of opiate use, as evidenced by positive urines, are equivalent between methadone and buprenorphine. There is strong evidence that buprenorphine is superior to placebo with respect to retention in treatment, and good evidence that buprenorphine is superior to placebo with respect to positive urine testing for opiates.

If inadequate, main reasons for recommending that the article not be cited as evidence	

Additional references if relevant
- Hser, Y-I, Evans E. et al. Long-term outcomes after randomization to buprenorphine/naloxone versus methadone in a multi-site trial. Addiction 2015; 111, 695–705