Critique author	Ed Whitney

Bibliographic Data	
Authors	Hale ME, Zimmerman TR et al
Title	Efficacy and safety of a hydrocodone extended-release tablet formulated with abuse-deterrence technology in patients with moderate-to-severe chronic low back pain.
PMID	26728648
Citation	J Opioid Manag. 2015 Nov-Dec;11(6):507-18
Other information if relevant	Registered at clinicaltrials.gov as NCT01789970

Methods	
Aim of study	In patients with chronic low back pain, to compare the efficacy and safety of an extended release, abuse-deterrent formulated hydrocodone versus placebo
Design	Randomized trial with a screening period of 7-14 days followed by an open-label titration period of up to 6 weeks followed by a double blind treatment period of up to 12 weeks

Participants	
Population from which participants are drawn	Patients age 18-80 with a history of moderate to severe low back pain for at least 3 months at screening
Setting (location and type of facility)	78 sites in the United States
Age	51.8
Sex	182 men and 189 women randomized

Total number of participants for whom outcome data were reported	625 enrolled in open label titration phase 254 withdrew during titration phase 371 were randomized following titration phase
Inclusion criteria	>= 3 months of low back pain
Exclusion criteria	- Taking >135 mg/day of oxycodone or equivalent during the 14 days before screening - Recent history (past 5 years) or current evidence of alcohol or substance abuse - Cardiopulmonary disease or other medical/psychiatric condition which would increase risks of opioid use - Diagnosis of any source of chronic pain other than the low back - Pregnancy or lactation - Treatment with an MAO inhibitor within 14 days of first dose of study drug
Other information if relevant	Patients could be opioid-naïve or opioid experienced, provided that they were taking between 10 and 135 mg of oxycodone or equivalent for 14 days before screening

Intervention Groups **Group 1**	Description as stated in report/paper
Group name	Hydrocodone ER
Number in group	191 (110 opioid naïve, 81 opioid experienced)
Description of intervention	- The first phase of treatment was an open-label titration period lasting up to 6 weeks during which each patient identified a dose of the study drug which provided optimal pain relief without unacceptable side effects - Opioid-naïve patients were begun on a dose of 15 mg every 12 hours, and opioid-experiences patients were begun on a dose equivalent to 50% of the opioid dose they were taking at enrollment - Rescue medication was permitted during dose titration, limited to hydrocodone immediate release/acetaminophen 5/325 mg not to exceed 2 tablets per day - Patients who attained an optimal dose during the titration period were then randomized and entered into the double-blind phase of the study, where they continued their optimal dose for 12 weeks
Duration of treatment period	12 weeks

Co-interventions if reported	Rescue medication permitted of immediate release hydrocodone/acetaminophen 5/325 mg, not to exceed 12 tablets (60 mg hydrocodone) per day
Additional information if relevant	Percent of patients with optimal hydrocodone doses every 12 hours were as follows: 30 mg 29%, 45 mg 32%, 60 mg 24%, 90 mg 16%

Intervention Groups **Group 2**	Description as stated in report/paper
Group name	Randomized withdrawal group
Number in group	179 (105 opioid-naïve; 75 opioid experienced)
Description of intervention	- The first phase of treatment was an open-label titration period lasting up to 6 weeks during which each patient identified a dose of the study drug which provided optimal pain relief without unacceptable side effects - Opioid-naïve patients were begun on a dose of 15 mg every 12 hours, and opioid-experiences patients were begun on a dose equivalent to 50% of the opioid dose they were taking at enrollment - Rescue medication was permitted during dose titration, limited to hydrocodone immediate release/acetaminophen 5/325 mg not to exceed 2 tablets per day - After the optimal dose had been attained, patients in the placebo group gradually and in a blinded fashion had an identical-appearing placebo substituted for hydrocodone over a period of two weeks - In the first week of the withdrawal period, the patients received one half of the optimal hydrocodone ER dose; in the second week, they received 15 mg of hydrocodone ER per day - After two weeks of withdrawal the patients were maintained on placebo for the remainder of the double-blind phase
Duration of treatment period	12 weeks
Co-interventions if reported	Rescue medication permitted of immediate release hydrocodone/acetaminophen 5/325 mg, not to exceed 12 tablets (60 mg hydrocodone) per day
Additional information if relevant	Percent of patients with optimal hydrocodone doses every 12 hours were as follows: 30 mg 36%, 45 mg 34%, 60 mg 17%, 90 mg 14%

Primary outcome	Description as stated in report/paper

Outcome name and criteria for definition	- Change from the end of the open-label titration to week 12 in the weekly average score of worst pain intensity (WPI) scores compared to baseline - Baseline WPI was defined as the average weekly WPI for the 7 days before randomization to double-blind treatment
Time points measured and/or reported	Weeks 1, 2, 8, and 12 Main analysis was at week 12
Differences between groups	- At screening, both groups had severe WPI scores (placebo 8.2, hydrocodone ER 8.1) - At 12 weeks, the placebo group had an increase of 0.74 points in WPI scores, compared to 0.11 in the hydrocodone ER group - The group difference in change of WPI was 0.63 points (95% CI 0.26 to 1.00) in favor of the hydrocodone ER group
Additional information if relevant	- Sensitivity analyses were carried out under different assumptions about missing values (best case versus worst case scenarios for the missing data) - The sensitivity analyses were robust, with results similar to those of the main analysis

Secondary outcomes	Description as stated in report/paper
Outcome name and criteria for definition	- Change from baseline in weekly average pain intensity (API) scores - Time to loss of efficacy, defined as discontinuation due to lack of efficacy or excessive use of rescue medication, defined as taking more than 15 mg per day for 10 or more days during any consecutive 14 days during the double-blind period - Percentage of patients with both >=30% increase in API from baseline to week 12 and an API score of 5 or greater at week 12 - Change from baseline to 12 weeks in the Roland-Morris Disability Questionnaire (RMDQ) - Safety as assessed by monitoring serious adverse events - Diversion and loss of study drug
Time points measured	Weeks 1, 2, 8, and 12 Main analysis was at week 12

Differences between groups	- Changes from baseline in API score differences were similar to the WPI score differences and were also in favor of hydrocodone ER (0.58 points, 95% CI from 0.25 to 0.91) - Percentage of patients with loss of efficacy was lower for hydrocodone ER (23%) than for placebo (30%), but this difference was not statistically significant - Percentage of patients with both >=30% increase in API from baseline to week 12 and an API score of 5 or greater at week 12 did not significantly differ between groups after controlling for multiple comparisons (19% for placebo and 13% for hydrocodone ER) - No group differences were apparent for changes in RMDQ - Similar percentages of patients took rescue medication (71% in the hydrocodone group and 81 % in the placebo group - Serious adverse events during the double-blind period were reported for 3 patients in the hydrocodone ER group and for 3 patients in the placebo group
Additional information if relevant	- Audiometry was done in both groups, with no differences in pure tone audiometry during the 12 week double blind period - Diversion and loss of study drug does not appear to have been a serious problem during the study period; out of 623 patients who received any dose of study drug, six patients were thought to have diverted hydrocodone ER at any time during the study and six patients were thought to have diverted hydrocodone immediate release which was dispensed as rescue medication

Conclusions	
Key conclusions of study authors	- Hydrocodone ER at a dose of 30-90 mg every 12 hours for a period of 12 weeks was more effective than placebo - While the difference in pain intensity may appear small, it is in line with other studies using the same design - The fact that rescue medication of up to 60 mg immediate release hydrocodone was permitted during the double-blind period may have prevented more placebo patients from having greater increases in pain scores than would have happened if no rescue medication had been permitted

Risk of bias assessment		
Domain	Risk of bias	Comments

	Low High Unclear	
Random sequence generation *(selection bias)*	Low	
Allocation concealment *(selection bias)*	Low	
Blinding of participants and personnel *(performance bias)*	Low	Placebo tablets were identical in appearance to hydrocodone tablets
Blinding of outcome assessment *(detection bias)*	Low	
Incomplete outcome data *(attrition bias)*	Low	82% of hydrocodone group completed the study, compared to 79% of the placebo group
Selective outcome reporting? *(reporting bias)*	Low	All outcomes appear to have been reported
Other bias	N/A	

Sponsorship if reported		
Study funding sources if reported	Teva Branded Pharmaceutic Products	
Possible conflicts of interest for study authors	First author is a consultant to and conducts clinical trials funded by Teva Pharmaceuticals	
Notes:		

- **Comments by DOWC staff**

- 625 patients started the open label titration phase of the study, and 371 (59%) attained an optimal hydrocodone dose and were randomized; 41% discontinued during the titration phase for adverse events, lack of efficacy, noncompliance, and other reasons
- The authors handled missing data by multiple imputation, which can present problems of bias, but the sensitivity analyses which were done probably prevented this potential problem from biasing the group comparisons
- The study ended at 12 weeks, with patients on hydrocodone ER taking between 30 and 90 mg every 12 hours; it is not clear if this is to be done indefinitely
- The primary outcome of worst pain intensity did favor the hydrocodone group, but the effect size was not of clinically important magnitude, and the percentages of patients with 30% exacerbations of pain were about equal between groups
- Approximately one percent of participants who received any tablets of hydrocodone were thought to have diverted the study drug, but there is little description of the methods for ascertaining this rate of diversion
- The study essentially repeats and confirms what is already known for opioid management of chronic low back pain, that it is more effective than placebo, but only by a small and clinically dubious amount
- The statistically significant effect size for the primary outcome was likely due to the fairly large sample size of the study, and the secondary outcomes were similar between groups
- The study drug did not improve function in comparison to placebo
- No report of global improvement (much better, better, same, worse, etc) was included

Assessment by DOWC staff	
Overall assessment as suitability of evidence for the guideline ☐ High quality x☐ Adequate ☐ Inadequate	Adequate for some evidence that extended release hydrocodone has a small and clinically unimportant advantage over placebo for relief of chronic low back pain among patients who are able to tolerate the drug, and that 40% of patients who begin taking the drug do not attain a dose which provides pain relief without unacceptable adverse effects. Hydrocodone ER does not appear to improve function in comparison with placebo.
If inadequate, main reasons for recommending that the article not be cited as evidence	