Critique author	**Ed Whitney**

Bibliographic Data	
Authors	Lee JH, Lee C-S
Title	A randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of the extended-release tramadol hydrochloride/acetaminophen fixed-dose combination tablet for the treatment of chronic low back pain.
PMID	24183364
Citation	Clin Ther. 2013 Nov;35(11);1830-40
Other information if relevant	

Methods	
Aim of study	To determine the effectiveness of a fixed-dose combination of tramadol 75mg/acetaminophen 650 mg in the treatment of chronic low back pain
Design	Phase III randomized clinical trial

Participants	
Population from which participants are drawn	Patients with chronic low back pain
Setting (location and type of facility)	15 participating clinical settings in South Korea
Age	60
Sex	183 women, 62 men
Total number of participants for whom outcome data were reported	245

Inclusion criteria	Age between 25 and 75, able t6o walk moderate to severe chronic low back pain of average intensity 4 or more on a 10 point scale despite the use of NSAIDS or COX-2 inhibitors, requiring analgesic medication for at least 3 months, taking a stable dose of NSAID or COX-2 drugs and willing to stay on the same dose throughout the study period
Exclusion criteria	Failure of tramadol treatment in the past, ingestion of tramadol or any opioid within 30 days of the start of the study, acetaminophen within 7 days of the study, or comorbidity with tumor, infection, fibromyalgia, more severe pain in any region of the body than the lower back, CRPS, cauda equina, proximal diabetic neuropathy, back surgery within 3 months, or steroid injection within 4 weeks
Other information if relevant	Patients started with a 7 day screening period during which they took a stable dose of NSAID/COX-2 drugs they had been using for pain control. Only patients who reported an average pain intensity of 4 or more over the past 48 hours were randomized to the double blind phase of the trial

Intervention Groups

Group 1	
Group name	Tramadol-acetaminophen extended release (TA-ER)
Number in group	125
Description of intervention	- Fixed-combination tablets of 75 mg tramadol with 650 mg acetaminophen - All patients started with a seven day titration period of taking one tablet at 8 AM for the first three days, then one tablet at 8 AM and 8 PM for four days - After the titration period, patients took TA-ER bid at 8 AM and 8 PM for another 22 days, not to exceed 4 tablets per day
Duration of treatment period	29 days
Co-interventions if reported	NSAID/COX-2 drugs which the patients had been taking prior to enrollment for control of pain
Additional information if relevant	

Group 2	
Group name	Placebo
Number in group	120

Description of intervention	- Placebo tablets identical in appearance to TA-ER, taken at the same titration schedule and same study period
Duration of treatment period	29 days
Co-interventions if reported	NSAID/COX-2 drugs which the patients had been taking prior to enrollment for control of pain
Additional information if relevant	

Primary outcome	
Outcome name and criteria for definition	Percentage of patients with a 30% or better change in 48-hour average pain intensity compared to baseline
Time points measured and/or reported	Day 8, 15, and 29 of the study
Differences between groups	- 57% of TA-ER patients with full data (49 of 85) met the criterion of 30% pain relief, compared with 41.1% (37 of 90) in the placebo group - Similarly, more TA-ER patients had a 50% pain reduction (32%) versus placebo (20%)
Additional information if relevant	

Secondary outcomes	
Outcome name and criteria for definition	Discontinuation of study medication Functional improvement on the Korean version of SF-36 Functional improvement on the Korean Oswestry Index
Time points measured	Days 7, 15, and 29

Differences between groups	- More discontinuations occurred with TA-ER than with placebo - 33 TA-ER patients discontinued: 24 for adverse events, 3 for withdrawal of patient consent, 5 for protocol violations, and 11 for other reasons - 16 placebo patients discontinued: 4 for adverse events, 5 for withdrawal of consent, 3 for protocol violations, 2 for other reasons - TA-ER patients reported greater improvement on the role-physical, the general health, and the reported health transition subscales of the SF-3 than did the placebo patients; the bodily pain, mental health, social function, and role-emotional subscales did not differ between groups - The Korean Oswestry scores did not significantly differ between groups
Additional information if relevant	- It appears that the withdrawals were especially common in the first 7 days of the double blind phase; 19.2% of the TA-ER group had treatment for 7 or fewer days, compared to 5.8% of placebo group patients

Conclusions	
Key conclusions of study authors	- The combination of tramadol and acetaminophen has a synergistic effect on pain relief in patients with chronic low back pain - The pharmacokinetic properties of TA-ER are more favorable than those of immediate-release tramadol/acetaminophen, and permit twice daily dosing rather than 4 times per day - The drug should not be used in patients with severe renal or hepatic impairment - TA-ER may be an appropriate replacement for the immediate-release combination

Risk of bias assessment		
Domain	Risk of bias Low High Unclear	Comments
Random sequence generation *(selection bias)*		Low

Allocation concealment *(selection bias)*		Low
Blinding of participants and personnel *(performance bias)*		Low
Blinding of outcome assessment *(detection bias)*		Low
Incomplete outcome data *(attrition bias)*		Uncertain—early attrition due to adverse effects was common in the TA-ER group, but the VAS pain data for these patients is not clearly accounted for (see comments below)
Selective outcome reporting? *(reporting bias)*		Low for main analysis, but duration of study is very short, and apparently effectiveness beyond one month was not of interest to the authors
Other bias		Co-interventions were allowed in the form of NSAID/COX-2 drugs, but there is a lack of data regarding how many patients in each group took these drugs, nor what doses they were taking

Sponsorship if reported		
Study funding sources if reported	Janssen Ltd	
Possible conflicts of interest for study authors	All authors have received research funding from Janssen Ltd but indicate no further conflicts of interest	
Notes:		

Comments by DOWC staff

- The initial analysis of the primary outcome data did not show a difference between TA-ER and placebo, and the data were re-analyzed using a 100% Source Data Verification (SDV) analysis, which detected protocol violations which had not appeared in the trial database
- The FDA recognizes SDV as a method of monitoring trial data by verifying trial data against case report forms; for example, SDV may verify a patient's report of "no hospitalizations" against other medical records to verify that none have taken place
- It seems more likely that SDV will be done when an industry-sponsored trial's initial analysis shows no difference between test drug and placebo than when the initial trial data are favorable to the product being tested
- The data analysis used intention-to-treat analysis only for the safety outcomes, and used a full analysis set (FAS) for the efficacy data
- The FDA recognizes FAS as consistent with the intention-to-treat principle when complete followup of all participants is difficult to achieve, such as when patients provide no data after having completed part of the trial; the FDA contrasts FAS with analysis of the per-protocol set, which does not conserve the intention-to-treat principle
- The FDA also recognizes that imputation models (such as last observation carried forward and more complex mathematical models) can be used to compensate for missing data when FAS is being done; no such models were employed in this study
- The patients continued on whatever doses of NSAID or COX-2 drug they had been taking prior to entry; however, these doses are not reported, and it is uncertain what other drugs patients were taking during the trial
- The Oswestry function scores were not different between TA-ER and placebo

Assessment by DOWC staff	
Overall assessment as suitability of evidence for the guideline ☐ High quality ☐ Adequate x☐ Inadequate	The study is inadequate for evidence that extended-release tramadol/acetaminophen in a fixed-dose combination of 75mg/650 mg is more effective than placebo in relieving chronic low back pain; it is not more effective in improving function compared to placebo
If inadequate, main reasons for recommending that the article not be cited as evidence	The re-analysis of trial data through source data verification when the initial analysis was not favorable to TA-ER appears likely to introduce bias, but apparently is within what the FDA allows in its Guidance to Industry documents. However, the excess dropouts in the TA-ER group due to adverse effects compromise the comparison, since it would have been possible to use either last observation carried forward or some other mathematical model to compensate for the dropouts, and it is likely that such an analysis would not have shown a significant treatment effect

Additional references if relevant
- FDA Guidance for Industry: E9 Statistical Principles for Clinical Trials. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073137.pdf - FDA Guidance for Industry: Oversight of Clinical Investigations —A Risk-Based Approach to Monitoring http://www.fda.gov/downloads/Drugs/.../Guidances/UCM269919.pdf