Critique author	**Ed Whitney**

Bibliographic Data	
Authors	Leng X, Li Z, et al
Title	Effectiveness and Safety of Transdermal Buprenorphine Versus Sustained-release Tramadol in Patients With Moderate to Severe Musculoskeletal Pain: An 8-Week, Randomized, Double-Blind, Double-Dummy, Multicenter, Active-controlled, Noninferiority Study.
PMID	25503600
Citation	Clin J Pain. 2015 Jul;31(7);612-20.
Other information if relevant	

Methods	
Aim of study	To determine the noninferiority of a buprenorphine transdermal system (BTDS) to oral sustained release tramadol
Design	Phase III noninferiority trial

Participants	
Population from which participants are drawn	Adults with moderate to severe musculoskeletal pain not adequately relieved with NSAIDs
Setting (location and type of facility)	Multiple centers in orthopedics and rheumatology departments in China
Age	57
Sex	83 men, 186 women

Total number of participants for whom outcome data were reported	269
Inclusion criteria	Age 18 to 80 with noncancer moderate to severe musculoskeletal pain for at least 4 weeks with inadequate pain relief taking NSAIDs or acetaminophen for at least 4 days per week
Exclusion criteria	Fibromyalgia, a history of inadequate pain relief from any opioid drug, frequent need for analgesia from other chronic disorders (headache, gout, diabetic neuropathy, rheumatoid arthritis), significant medical comorbidity, , history of substance abuse, intolerance to study medications, previous participation in any BTDS study
Other information if relevant	Osteoarthritis and intervertebral disc disease were the most common reasons for enrollment All patients were withdrawn from pre-study analgesics at the time of enrollment

Intervention Groups

Group 1	
Group name	BTDS
Number in group	141
Description of intervention	- BTDS 7-day system with possible doses of 5, 10, or 20 mcg/hour - Initial dose was 5 mcg/hour with a 3 week titration period, during which the selection of doses was based on the investigators' assessments general considerations regarding pain management - Following titration period, a 5 week maintenance period was done in which the titrated dose was continued - Each patient taking BTDS also took tramadol placebo tablets identical in appearance to the tramadol tablets taken by the other randomized group, and the blinding was maintained throughout the study
Duration of treatment period	9 weeks
Co-interventions if reported	Acetaminophen as a rescue medication not to exceed 4 g/day during the titration phase and not to exceed 2 g/d during the maintenance phase
Additional information if relevant	Both groups took the drug for their group and the placebo of the other group (double blind double dummy design)

Group 2	
Group name	Sustained release tramadol
Number in group	139
Description of intervention	- SR tramadol in the form of 100 mg tablets at doses of 200, 300, and 400 mg/day - Titration phase was same as the BTDS group, lasting 3 weeks with investigator deciding dose changes based on principles of pain management - Similar to BTDS group, a maintenance phase lasted 5 weeks - A placebo BTDS patch, identical in appearance to the true patch, was applied by all patients throughout the study
Duration of treatment period	9 weeks
Co-interventions if reported	Acetaminophen as a rescue medication not to exceed 4 g/day during the titration phase and not to exceed 2 g/d during the maintenance phase
Additional information if relevant	

Primary outcome	
Outcome name and criteria for definition	- Pain during the preceding week, measured at treatment completion using a 10 point VAS
Time points measured and/or reported	At the end of the maintenance period of the trial
Differences between groups	- The noninferiority margin was set by protocol as VAS within +/- 1.5 cm, which was considered the threshold for a clinically meaningful difference - Both groups had clinically meaningful pain decreases during the study; the baseline VAS for BTDS was 6.44 versus 6.53 for tramadol - The mean VAS at study completion was 3.14 for BTDS versus 2.53 for tramadol - The VAS decreases were 3.30 for BTDS versus 3.75 for tramadol - The 95% confidence interval for the group differences in VAS improvement were between -0.08 and 0.99 cm, which fell within the 1.5 cm noninferiority margin in the protocol

Additional information if relevant	

Secondary outcomes	
Outcome name and criteria for definition	- Withdrawals from the study: 40 for BTDS (29 due to adverse events) and 33 for tramadol (25 for adverse events) - Sleep improvements were equal between groups: good or very good sleep was reported at the end of the study in 68% of BTDS patients and in 69% of tramadol patients - Use of acetaminophen as a rescue medication was also balanced between the two groups
Time points measured	Baseline and at the end of treatment
Differences between groups	As above, all group comparisons were within noninferiority margins for the secondary outcomes
Additional information if relevant	70% of patients in both groups expressed a preference for a 7 day patch over twice daily oral tablets, due to greater convenience of administration of the patch

Conclusions	
Key conclusions of study authors	- BTDS is noninferior to sustained release tramadol for the relief of moderate to severe musculoskeletal pain - The two drugs had equal safety profiles with equal occurrences of adverse events - There was not a placebo group against which to compare the effectiveness of either drug, but the goal of the study was not to show superiority or BTDS over placebo, but to show its noninferiority to sustained release tramadol

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 (double blind double dummy design was maintained throughout the study)
Blinding of outcome assessment *(detection bias)*		Low
Incomplete outcome data *(attrition bias)*		Low
Selective outcome reporting? *(reporting bias)*		Low
Other bias		

Sponsorship if reported		
Study funding sources if reported	Mundipharma Ltd of China	
Possible conflicts of interest for study authors	The first author, who was the principal investigator, declared no conflict of interest The two statisticians who analyzed the data received payments from the study sponsor for their work The other authors declared no conflict of interest	
Notes:		

Comments by DOWC staff

- The study appears to conform to the general guidance standards which the FDA sets for noninferiority studies
- Noninferiority studies are often done when a new treatment offers advantages over an established drug with respect to such considerations as convenience of dosing, safety profiles, cost, and occurrence of drug interactions
- The patients in both groups expressed a preference for the patch in terms of ease of administration, but it is not clear how strong this preference was, how the information was elicited (probably from interviews with possibly biased investigators)
- If BTDS is noninferior to tramadol, it is not clear which patients should be treated with it rather than with tramadol; this would probably be a small minority of patients with swallowing difficulties and severe renal or hepatic dysfunction
- The elimination of tramadol is affected by renal and liver disease, but the FDA package insert states that this becomes a consideration with creatinine clearance less than 30 ml/min or with cirrhosis of the liver
- As is generally the case with Phase III studies, the methodology is of high quality, and the difficulties arise with deciding on the relevance and application of the results to a particular patient population
- Global impression of pain relief may be more relevant than a comparison of mean VAS data due to the bimodal distribution of VAS numbers; these outcomes were also equal between groups, even though the actual data were not reported
- The proportion of patients with a 30% or a 50% pain reduction was not reported, even though this is useful information and is commonly reported in other studies of pharmacological treatment of pain

Assessment by DOWC staff	
Overall assessment as suitability of evidence for the guideline x☐ High quality ☐ Adequate ☐ Inadequate	High quality Phase III study showing that transdermal buprenorphine is noninferior to oral tramadol in the treatment of moderate to severe musculoskeletal pain arising from conditions like osteoarthritis and low back pain. The population of patients for whom it is more appropriate than tramadol is not established, but would need to be determined on an individual patient basis if there are clear reasons not to use oral tramadol.
If inadequate, main reasons for recommending that the article not be cited as evidence	

Additional references if relevant

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