Critique author	**Ed Whitney**

Bibliographic Data	
Authors	Boureau F, Legallicier P, Kabir-Ahmadi M.
Title	Tramadol in post-herpetic neuralgia: a randomized, double-blind, placebo-controlled trial
PMID	12855342
Citation	Pain. 2003 Jul;104(1-2):323-31.
Other information if relevant	

Methods	
Aim of study	To assess the safety and effectiveness of sustained release tramadol in patients with post-herpetic neuralgia (PHN)
Design	Randomized clinical trial

Participants	
Population from which participants are drawn	Outpatients consulting general practitioners for pain arising from a diagnosis of PHN
Setting (location and type of facility)	A multidisciplinary pain treatment center in Paris
Age	67
Sex	35 men, 92 women
Total number of participants for whom outcome data were reported	127 patients randomized Data reported on 108 patients in a per protocol (PP) analysis (the main analysis) Intention to treat analysis (ITT) was also done with 125 patients
Inclusion criteria	Age 18-85 with symptoms of PHN for at least 3 months but less than 12 months, with spontaneous rating of at least 40 on a VAS from 0-100

Exclusion criteria	Current or past symptoms or past history of depression, seizures, illicit drug abuse or CNS depressant drug abuse, recent CNS trauma, severe hepatic, renal, cardiac or respiratory pathology, hypersensitivity to tramadol or to opioids, pregnancy, MAO inhibitors within 15 days prior to the inclusion visit, antidepressants, anticonvulsants, opioid analgesics or local/general anaesthetics within 7 days prior to the inclusion visit
Other information if relevant	The PP analysis was the primary population for comparing groups, but ITT was also adequately reported on the main outcome

Intervention Groups

Group 1	
Group name	Tramadol
Number in group	53
Description of intervention	100 mg tablets were given with a titration schedule from one tablet per day in the evening as a starting dose, which could be increased to 4 per day in patients under 75 and 3 per day in patients over 75, with at least 48 to 72 hours required between dose increases
Duration of treatment period	6 weeks
Co-interventions if reported	Acetaminophen at a maximal daily dose of 3 g was permitted during the study as a rescue medication
Additional information if relevant	

Group 2	
Group name	Placebo
Number in group	55
Description of intervention	Identical appearing tablets, without description of titration schedule, but presumably conducted under the same rules as that for tramadol
Duration of treatment period	6 weeks
Co-interventions if reported	Acetaminophen at a maximal daily dose of 3 g was permitted during the study as a rescue medication
Additional information if relevant	

Primary outcome	
Outcome name and criteria for definition	VAS pain intensity at the end of the trial (day 43), adjusted for pain intensity on day 1 (analysis of covariance analysis with treatment group and baseline score as covariates)
Time points measured and/or reported	VAS scores were collected on days 1, 8, 15, 22, and 43 This allowed the authors to use repeated measures analysis of variance for the interim scores, but the conclusions are based on the day 43 scores
Differences between groups	- Tramadol was more effective than placebo on the PP analysis - Tramadol pain intensity on day 1 was 60.8 on the PP analysis; for placebo, the pain intensity on day 1 was 60.0 - The pain intensity on day 43, adjusted for the pain on day 1, was 19.9 for the tramadol group and 28.5 for the placebo group - The adjusted pain difference on day 43 was 8.6 points in favor of tramadol (95% confidence interval 0.1 to 17.1) - The ITT analysis was similar to the PP analysis; the adjusted pain score difference on day 43 was 9.0 points in favor of tramadol (95% CI 0.9 to 16.9)
Additional information if relevant	The mean pain duration was similar in both groups; it was 6.7 months for tramadol and 7.0 months for placebo

Secondary outcomes	
Outcome name and criteria for definition	- Pain intensity on a 5 point verbal rating scale (none, mild, moderate, severe, and extremely severe) did not distinguish tramadol from placebo - Fewer tramadol patients (26%) used acetaminophen than placebo patients (45%) - 10 patients assigned to tramadol had protocol deviations, versus 7 protocol deviations in the placebo group - 19 tramadol patients and 20 placebo patients reported a total of 59 adverse events; a physician judged the adverse events to be treatment related in 13 tramadol patients and in 6 placebo patients - Nausea was reported in 12.5% of the tramadol group and in3.2% of the placebo group - Constipation was reported in 4.7% of tramadol patients
Time points measured	Days 1, 8, 15, 22, and 43

Differences between groups	As noted above; adverse events were more frequent with tramadol than with placebo 6 tramadol patients withdrew from the study early due to adverse events A total of 16 patients discontinued the study prematurely (11 in the tramadol and 5 in the placebo group)
Additional information if relevant	A general quality of life measurement (the Nottingham scale) was also used as a secondary outcome, and both groups had equal improvements from day 1 to day 43

Conclusions	
Key conclusions of study authors	- Tramadol administered over a 6 week period was effective on the primary criterion of pain intensity in both the PP and ITT analyses, and was safe in these patients - Spontaneous pain resolution reflects the natural history of PHN; this feature of the clinical course of PHN shows why a parallel group RCT is preferable to a crossover RCT design - Some patients with PHN clearly benefit from tramadol, which has both opioid and monoaminergic mechanisms of action

Risk of bias assessment		
Domain	Risk of bias Low High Unclear	Comments
Random sequence generation *(selection bias)*	Low	
Allocation concealment *(selection bias)*	Low	Randomization was done with a computer-generated four-block centralized list
Blinding of participants and personnel *(performance bias)*	Low	Tramadol and placebo were given in the form of identical-appearing tablets

Blinding of outcome assessment *(detection bias)*	Low	VAS is self-reported, but the design of the placebo tablet is likely to reduce the risk of bias for this outcome
Incomplete outcome data *(attrition bias)*	Low	The per-protocol analysis was the main outcome measure, departing from the generally preferred intention to treat analysis; however, the results for both analyses are given, and the ITT analysis was equal to the PP analysis
Selective outcome reporting? *(reporting bias)*	Unclear	The primary outcome was probably the one used in the main analysis, but the trial was not registered, and this was not a near universal practice as it is in 2016
Other bias		

Sponsorship if reported		
Study funding sources if reported	No information	
Possible conflicts of interest for study authors	No information	
Notes: - In 2003, current standards for reporting conflicts of interest were not all in place - Tramadol came on the market in 1977 in Germany, and may have been generic in France in 2003 when the study was published		

Comments by DOWC staff

- Although most sources of bias are adequately controlled, the primary outcome was not completely clear; however, it was probably the 43 day average VAS which was reported as primary
- Some of the analyses appear to be oriented toward the pursuit of nominal statistical significance, as evidenced by a p value for the principal analysis of 0.0499, which represents a clinically small treatment difference between groups
- The ITT tramadol-placebo pain difference of 9 points on the 100 point VAS is of little clinical importance, but the improvement in both groups was clinically important, and much of that improvement is likely to reflect the natural history of the underlying condition, which could mask a clinically relevant therapeutic benefit of tramadol
- The authors did a sample size calculation using generally accepted methods (effect size, type 1 and type 2 error, and estimated standard deviation) which use parametric statistics, assuming a normal distribution of pain scores; since pain scores probably do not distribute themselves in a normal curve, the power of the study is uncertain
- There are two "Nottingham" quality of life scales, one of which has a higher score as the quality of life improves, and the other of which has a lower score as quality improves
- The Nottingham scale used in the outcome analysis was probably that of Hunt et al 1980; the study does not furnish a reference for the scale which was reported

Assessment by DOWC staff	
Overall assessment as suitability of evidence for the guideline ☐ High quality ☒ Adequate ☐ Inadequate	A methodologically adequate study which supports some evidence that tramadol yields a short term analgesic response of little clinical importance relative to placebo in postherpetic neuralgia which has been symptom for approximately 6 months
If inadequate, main reasons for recommending that the article not be cited as evidence	

Additional references if relevant

- Hunt SM, McKenna SP, et al. A quantitative approach to perceived health status: A validation study. Journal of Epidemiology & Community Health 1980; 34 (4): 281–6