Critique author	**Ed Whitney**

Bibliographic Data	
Authors	Campbell CM, Kipnes MS, et al
Title	Randomized control trial of topical clonidine for treatment of painful diabetic neuropathy
PMID	22683276
Citation	Pain 2012;153:1815-1823
Other information if relevant	

Methods	
Aim of study	To assess the effectiveness of topical clonidine in the setting of painful diabetic neuropathy
Design	Randomized clinical trial

Participants	
Population from which participants are drawn	Patients with either type 1 or type 2 diabetes mellitus who had painful neuropathy affecting the feet in a stocking type distribution
Setting (location and type of facility)	Multiple centers in the United States
Age	58
Sex	93 women, 86 men
Total number of participants for whom outcome data were reported	179

Inclusion criteria	Between 18 and 80 years of age with pain in a symmetrical stocking distribution neuropathy in the lower extremities, lasting at least 6 months but less than 5 years Average daily pain score of at least 4 on a scale from 0 to 10 the baseline phase Stable glycemic control regimen for at least 3 months Stable analgesic regimen for at least 21 days prior to randomization Willingness to maintain current medications at the same dose throughout the study
Exclusion criteria	Other chronic pain with greater intensity than their PDN pain Other chronic pain within the region of PDN Any serious or unstable medical or psychological condition Hypotension History of illicit drug or alcohol abuse within a year Cognitive or language difficulties that would impair understanding/completion of the assessment instruments Pregnant or lactating females, planning to become pregnant, or using unreliable means of birth control Received other experimental drugs within 2 months of randomization Prior use of topical clonidine gel Open lesions or skin conditions in the area of gel application Known sensitivity or intolerance to clonidine
Other information if relevant	- Although it was not used as an inclusion criterion, the investigators applied 0.1% capsaicin over the pretibial area during screening, and the participants were asked to record their numerical pain response to the application - This was done in order to detect the severity of the small fiber neuropathy - 97 participants also consented to a 3 mm skin punch biopsy which was sent for quantitation of intraepidermal nerve fiber density, which was compared with the capsaicin response

Intervention Groups

Group 1	
Group name	Clonidine
Number in group	89

Description of intervention	- Self-administration of topical clonidine gel three times per day - A single dose consisted of the amount of gel dispensed with one complete pump from a metered dose bottle, which was applied to both feet evenly to the toes, between the toes, and the top and bottom of each foot extending up to the ankle - The daily dose of clonidine was 3.9 mg when used in this manner
Duration of treatment period	12 weeks
Co-interventions if reported	
Additional information if relevant	

Group 2	
Group name	Placebo gel
Number in group	90
Description of intervention	Identical to the clonidine group, except that the metered dose gel contained no clonidine
Duration of treatment period	12 weeks
Co-interventions if reported	
Additional information if relevant	

Primary outcome	
Outcome name and criteria for definition	- Change in pain scores on the Numerical Pain Rating Scale (NPRS) - Responder rates as defined by a 30% decrease in pain from baseline
Time points measured and/or reported	Patients returned to clinic for visits at weeks 1, 2, 4, 6, 8, 10, and 12 The primary outcome was reported at the 12 week visit

Differences between groups	- The clonidine group had a decrease in NPRS of 2.3 points, while the placebo group had a decrease of 1.7 points, and the difference was not statistically significant (p=0.07) - The responder rate in the clonidine group was 48%, and the responder rate in the placebo group was 40%; these response rates were statistically equivalent (p=0.48)
Additional information if relevant	- Although the comparison was not in the protocol when the trial was registered, the authors reported the results separately for the subgroups who did and did not have a pain response to pretibial capsaicin - The 99 patients who did not detect capsaicin also had no difference in response to capsaicin versus placebo - The patients who detected any level of pain from capsaicin (capsaicin response >0) did have a statistically significant difference in response between clonidine and placebo, with the average difference being 0.9 points on the NPRS - In patients who had a capsaicin response >= 2 had a mean pain response difference of 1.2 points on the NPRS - Patients who had a capsaicin response had significantly greater nerve fiber density on the punch biopsies taken at baseline

Secondary outcomes	
Outcome name and criteria for definition	- Brief pain inventory - Chronic pain sleep inventory - Global impression of change as recorded by both patient and clinician - Hospital Anxiety and Depression Scale
Time points measured	12 weeks for the main analysis
Differences between groups	- No group differences were reported for the secondary outcomes - No adverse events occurred with clonidine gel
Additional information if relevant	

Conclusions	
Key conclusions of study authors	- Treatment with topical clonidine reduces pain from diabetic peripheral neuropathy in a manner which depends on the relative level of functionality of the nociceptors in the skin - Other bedside tests of sensory function, such as vibration and thermal testing, did not correlate with the response to clonidine, and are best seen as screening tests rather than sensitive tests of nociceptor function - Many attempts at phenotyping neuropathic pain have failed, and the response to capsaicin should be included in future clinical trials

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)*	Low	

Selective outcome reporting? *(reporting bias)*	Low	- Although the subgroup analysis was not in the protocol registered at clinicaltrials.gov, the authors reported that this analysis was in the statistical analysis plan - It is rare for clinicaltrials.gov to display statistical analysis plans when trials are registered - Because the capsaicin test was given to all patients at the start of the study, it is very likely that the subgroup analysis was pre-planned, and therefore not at risk of selective outcome reporting bias
Other bias		

Sponsorship if reported		
Study funding sources if reported	Arcion Therapeutics	
Possible conflicts of interest for study authors	The first author was awarded a travel grant from Arcion to present and attend the Neuropathic Pain Conference in 2008	
Notes:		

Comments by DOWC staff

- A well-planned and executed study which helps to address more than one pertinent question regarding the management of neuropathic pain
- The overall effect of clonidine was not statistically different from placebo
- However, the response in the group which had a pain response to capsaicin was statistically significant and probably clinically meaningful as the capsaicin response increases
- As noted above, the subgroup analysis was almost certainly preplanned and therefore supportable as evidence
- The capsaicin response is informative because it has the potential to control much of the heterogeneity which often clouds comparisons between active drugs and placebos

Assessment by DOWC staff	

Overall assessment as suitability of evidence for the guideline ☒ High quality ☐ Adequate ☐ Inadequate	High quality study supporting good evidence that topical clonidine gel 0.1% is likely to alleviate pain from diabetic peripheral neuropathy in patients who display a nociceptive response to the application of 0.1% capsaicin applied to the pretibial area. It is likely that patients who do not display a pain response to pretibial capsaicin are not likely to have a clinically meaningful analgesic response to clonidine gel. It is unknown if this screening test applies to other types of neuropathic pain.
If inadequate, main reasons for recommending that the article not be cited as evidence	

Additional references if relevant
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