Critique author	**Ed Whitney**

Bibliographic Data	
Authors	Deer TR, Levy RM, et al.
Title	Dorsal root ganglion stimulation yielded higher treatment success rate for CRPS and causalgia at 3 and 12 months: randomized comparative trial
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Other information if relevant	The manuscript has been accepted for publication, but the date of print publication is not announced

Methods	
Aim of study	In patients with CRPS I and II, to compare the effectiveness of dorsal root ganglion stimulation (DRG) versus conventional spinal cord stimulation (SCS)
Design	Randomized non-inferiority clinical trial

Participants	
Population from which participants are drawn	Patients with chronic, intractable lower limb pain from CRPS or causalgia
Setting (location and type of facility)	Multiple centers in the United States
Age	52
Sex	78 women, 74 men
Total number of participants for whom outcome data were reported	152 randomized; 115 implanted, 113 with 3 month followup data

Inclusion criteria	Age 22-75 with chronic, intractable lower limb pain for at least 6 months, a diagnosis of CRPS or causalgia, pain VAS minimum of 60/100 in the lower limb, failure of at least 2 analgesics from 2 different drug classes, stable neurologic function in past 30 days, able to comply with followup schedule and protocol, and suitability for implant in the opinion of the investigator
Exclusion criteria	Dominant back pain, escalating or changing pain in past 30 days, pregnancy or unwillingness to use birth control, medical litigation including workers compensation, corticosteroid therapy at site of intended implantation in past 30 days, radiofrequency treatment of intended DRG in past 3 months, previous failure of SCS, current implantable device such as pacemaker or intrathecal drug pump, pain only in cervical distribution, coagulation disorder or anticoagulant use, cancer in past 2 years, systemic infection
Other information if relevant	- The study was designed as a non-inferiority trial, in which the new treatment (DRG) was hypothesized to be non-inferior to a standard treatment (SCS) - The non-inferiority margin was 10% with respect to the primary endpoint in which successful treatment was determined 3 months after the permanent implant was placed, and success meant that the patient had a 50% pain reduction without a stimulation-related neurological deficit - This means that if the success rate of the DRG was less successful than the rate for SCS, but the difference between SCS and DRG was less than 10%, the DRG was declared to be non-inferior to SCS - If the non-inferiority margin was met, the study was to be analyzed as a superiority trial, in which DRG could be declared superior to SCS, provided that the p value for the difference was less than 0.025

Intervention Groups

Group 1	
Group name	DRG
Number in group	76

Description of intervention	- All patients randomized to DRG were first given a temporary trial lasting from 3 to 30 days depending on the practice protocols of the participating centers; the mean trial duration was 5.8 days - Successful trial stimulation was defined as at least a 50% reduction in lower limb pain and a desire to proceed to a permanent implant - Patients for whom the trial failed were counted as treatment failures - DRG stimulation was delivered by a system composed of percutaneous leads, an external trial pulse generator, and an implantable pulse generator - DRG leads were placed in the lateral epidural space near the target DRG at levels from T10 to S2, depending on the dermatome corresponding to the lower limb pain
Duration of treatment period	- The primary endpoint was measured at 3 months, but the observation period for the trial was 12 months
Co-interventions if reported	- Patients were not allowed to change their maximum daily dose of pain medication during the 3 month period between placement of the implant and assessment of success or failure at the 3 month followup
Additional information if relevant	

Group 2	
Group name	SCS
Number in group	76
Description of intervention	- The protocol for a trial of SCS was the same as for DRG, and the average trial duration was also 5.8 days as for the DRG group - Permanent implantation of SCS was done with a commercially available system which was programmed by personnel experienced with the device - SCS leads were placed in the medial or paramedial epidural space with the most caudal lead was not caudal to the top of the L1 vertebral body
Duration of treatment period	- The primary endpoint was measured at 3 months, but the observation period for the trial was 12 months

Co-interventions if reported	- Patients were not allowed to change their maximum daily dose of pain medication during the 3 month period between placement of the implant and assessment of success or failure at the 3 month followup
Additional information if relevant	Approximately 59% of the patients in each group had CRPS and about 41% had causalgia

Primary outcome	
Outcome name and criteria for definition	- Successful treatment was defined as a 50% pain reduction without implant-related neurological deficits
Time points measured and/or reported	- 3, 6, and 12 months; primary comparison done at 3 months
Differences between groups	- The success rate for DRG at 3 months was 81.2%; 56/69 - The success rate for SCS at 3 months was 55.7%; 39/70 - These results showed not only non-inferiority, but statistical superiority of DRG over SCS - The 12 month followup continued to show superiority of DRG (79.3% success) over SCS (53.0%) - The comparative success rates were essentially the same for CRPS and for causalgia; the treatment difference did not depend on the condition being treated
Additional information if relevant	

Secondary outcomes	
Outcome name and criteria for definition	- There was one secondary endpoint and there were numerous additional endpoints - The secondary endpoint designated by the authors was postural variation in perceived paresthesia intensity between supine and upright positions on an 11 point scale of 0 to 10
Time points measured	3 months

Differences between groups	- The DRG patients had significantly less postural variation in perceived paresthesia than SCS patients - The DRG patients had a mean supine-upright paresthesia difference of - 0.1 points; the SCS patients had a difference of 1.8 points
Additional information if relevant	- Data from the safety analyses did not differ statistically between groups, but there were 2 infections in the SCS group requiring explantation; there were no stimulation-related neurological deficits in either group - Overall patient satisfaction at 3 months was a mean of 8.8 for DRG and 8.3 for SCS, a statistically equivalent level of satisfaction with treatment - Mean baseline VAS for DRG was 80.6; mean VAS at 3 months was 13.1 - Mean baseline VAS for SCS was 80.7; mean VAS at 3 months was 23.8

Conclusions	
Key conclusions of study authors	- Neuromodulation with SCS or with DRG offers benefits to patients with CRPS and causalgia who have exhausted other treatment options - SCS has a limited ability to target discrete focal anatomical regions of pain that commonly occur with CRPS and causalgia - DRG stimulation provides an effective alternative to SCS and provides precision targeting that improves patient outcomes

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)*	High	But see below
Blinding of outcome assessment *(detection bias)*	Unclear	Although both groups knew what treatment they had received, it is difficult to predict the likely direction of any resulting bias in the absence of more information about the expectations of the randomized groups. As the "novel" treatment option, DRG may have had an advantage
Incomplete outcome data *(attrition bias)*	Low	
Selective outcome reporting? *(reporting bias)*	Low	The study protocol is on file at clinicaltrials.gov and the primary outcome in the protocol matches the primary outcome in the report
Other bias		

Sponsorship if reported		
Study funding sources if reported	Spinal Modulation, LLC, a wholly owned company of St. Jude Medical	
Possible conflicts of interest for study authors	All authors were paid by Spinal Modulation, LLC as investigators for the clinical trial	
Notes:		

Comments by DOWC staff

- The overall design, conduct, and reporting of the trial is high quality
- A few numerical issues are slightly unclear, but do not negate the basic comparison of primary outcomes
- Specifically, the flow diagram of randomized patients has 76 patients allocated to DRG, of whom 3 refused the trial (therefore being excluded from the denominator) and 73 completed the trial visit, remaining in the denominator
- The denominator for the 3 month success rate for DRG is 69 patients, which should represent all patients who had the trial, counting the trial failures as treatment failures for each group
- If 73 patients completed the DRG trial visit, it would be necessary to account for the 4 patients who completed that visit but did not become part of the denominator of 69 for the primary outcome reporting
- Of the 73 patients who completed the trial visit, 6 failed the trial phase (clearly these become part of the denominator), 2 refused the implant, 3 withdrew, and 1 exited due to a related adverse event
- The 2 who refused the implant would not have had the trial and would not enter the denominator; this would leave 71 patients to be accounted for, 2 of whom have to be excluded in order to reduce the denominator to 69 patients
- The 1 patient who exited due to a related adverse event should be counted as a trial failure and remain in the denominator
- This leaves the reader with the 3 patients who "withdrew" without elaboration of the reasons
- If all 3 of these were excluded, the denominator would be reduced to 68; if all three remain, the denominator stays at 71
- Thus, it is not clear how the denominator was arrived at
- There are many additional variables which affect the patient response to neuromodulation, of which the implanted device is one; however, the programming of the device is another variable, and variations in programming could become a factor in treatment success
- There is one factor which adds biological plausibility to the clinical differences which were observed for the DRG group, namely, the fact that each ganglion maps to a single dermatome

Assessment by DOWC staff	
Overall assessment as suitability of evidence for the guideline ☐ High quality ☒ Adequate ☐ Inadequate	A well conducted and well reported clinical trial. An unclear risk of bias with respect to blinding makes the degree of bias unclear. It supports good evidence that dorsal root ganglion stimulation is non-inferior to conventional spinal cord stimulation with respect to pain relief. There is some evidence that DRG stimulation is superior to SCS with respect to pain relief for up to 12 months after implantation. Neurological deficits related to stimulation with either device appear to be rare.

If inadequate, main reasons for recommending that the article not be cited as evidence	

Additional references if relevant
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