Critique author	**Ed Whitney**

Bibliographic Data	
Authors	Perruchoud C, Eldabe S, et al.
Title	Analgesic efficacy of high-frequency spinal cord stimulation: A randomized double-blind placebo-controlled study.
PMID	23425338
Citation	Neuromodulation 2013;16:363-369.
Other information if relevant	

Methods	
Aim of study	To compare the effectiveness of high frequency spinal cord stimulation (SCS) with that of sham SCS
Design	Randomized crossover study

Participants	
Population from which participants are drawn	Patients who have already been treated with a conventional SCS device
Setting (location and type of facility)	Departments of Anesthesia and Pain Management at hospitals in Switzerland and in the UK
Age	54
Sex	16 men, 17 women
Total number of participants for whom outcome data were reported	33 (out of 40 who were recruited for the study but were not randomized)
Inclusion criteria	Ability to understand the study and willingness to be treated with SCS for chronic low back pain radiating to one or both legs, having current stable pain control with a previously implanted Medtronic impulse generator

Exclusion criteria	Inability to understand the study or to keep a pain diary
Other information if relevant	The study was a crossover study, in which both interventions were given to each patient and the order of the interventions was randomized

Intervention Groups

Group 1	
Group name	Sequence 1
Number in group	17
Description of intervention	- All patients had a run-in period of 2 weeks of conventional SCS for collection of baseline data - After the 2 week baseline period, an unblinded investigator programmed the SCS device to cover as much as possible of the pain area with conventional stimulation, followed by increasing the frequency to 5 KHz, followed by increasing the amplitude o the sensory threshold, followed by decreasing the amplitude until paresthesias disappear - After these four steps, the pulse width was adjusted to 60 microseconds under high-frequency SCS (HFSCS), which continued for two weeks - After 2 weeks of HFSCS, conventional SCS was resumed for 2 weeks - After 2 weeks of conventional SCS, the stimulator was switched off, producing a sham SCS condition for two weeks, leading to the end of the study - After 2 weeks of sham SCS, the study data were collected, and conventional SCS was resumed
Duration of treatment period	2 weeks for each treatment condition as outline above
Co-interventions if reported	Patients had the opportunity to switch the device off during an emergency, and the device shut-off was detected by the study programmer through a time stamp on the device
Additional information if relevant	Blinding was maintained during sham SCS by programming the device with a current leak so that recharging time and frequency were equivalent to those of true SCS

Group 2	
Group name	Sequence 2
Number in group	16

Description of intervention	- The conditions were identical to those in Sequence 1, except that instead of setting the pulse width to 60 microseconds after adjusting the frequency and amplitude of the device, the SCS was switched off
Duration of treatment period	2 weeks for each treatment condition as outline above
Co-interventions if reported	Same as Sequence 1
Additional information if relevant	Blinding was maintained as it was in Sequence 1 with a programmed current leak during the sham SCS condition

Primary outcome	
Outcome name and criteria for definition	- Patient global impression of change (PGIC) - This was scored on a seven point scale in which the patient compares current pain control with the pain control achieved under conditions which were present at the end of the baseline run-in period (after 2 weeks of conventional SCS) - The seven responses of the PGIC are (1) very much improved, (2) much improved, (3) minimally improved, (4) no change, (5) minimally worse, (6) much worse, and (7) very much worse - The PGIC scores were dichotomized into “responder” and “non-responder” categories, in which a responder was a patient who reported at least “minimally improved” compared to pain under baseline conventional SCS
Time points measured and/or reported	At each of 5 visits: after randomization, after 2 weeks of conventional SCS, after 2 weeks of the first experimental treatment period of either HFSCS or sham SCS, after two more weeks of conventional SCS between experimental treatment periods, and after two weeks of a second experimental treatment period in which the HFSCS and sham SCS interventions were reversed from those of the first experimental treatment period

Differences between groups	- For sequence 1 (HFSCS first), 9 of 17 patients responded to HFSCS during the first treatment period, and 2 of these 17 patients responded to sham SCS during the second treatment period - For sequence 2 (sham first), 8 of 16 patients responded to sham SCS in the first treatment period, and 5 of these 16 responded to HFSCS during the second treatment period - Thus, during the first treatment period, 17 out of 33 (51.5%) patients were responders to whichever treatment they received, but during the second treatment period, 7 out of 33 (21.2%) patients were responders to whatever treatment they received - Overall, 14/33 patients responded to HFSCS, and 10/33 responded to sham SCS
Additional information if relevant	- 8 patients who responded to sham SCS during the first treatment period were debriefed and asked which treatment they thought they were on; 4 thought they were on sham and 4 thought they were on HFSCS

Secondary outcomes	
Outcome name and criteria for definition	- Pain VAS - EQ-5D as a quality of life measure - Overall medication use
Time points measured	At each evaluation visit
Differences between groups	- Baseline VAS was 4.0 for the entire study cohort; the mean pain VAS was 4.26 on sham versus 4.35 on HFSCS - EQ-5D did not differ as a function of treatment condition - Overall medication use did not change
Additional information if relevant	When asked which treatment they were receiving, 45% guessed correctly at the end of the first treatment period and 55% guessed correctly at the end of the second treatment period, which was what can be expected by chance

Conclusions	
Key conclusions of study authors	- The effect of HFSCS appears to be equivalent to that of sham SCS, and the order of the treatment sequence, and not the nature of the therapy, appears to dictate the treatment effect - The results were obtained in patients who had already been using a conventional SCS, and cannot be applied to chronic back pain patients who are treatment-naïve and would be using SCS for the first time - The intensity of the treatment was 5KHz, which is a subthreshold amount, and the study was designed on the assumption that this dose would produce analgesia without paresthesia - The short treatment period was a possible factor in the results of the study, since there may be a considerable carryover effect from the periods of conventional SCS which preceded each experimental treatment period

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	The sham treatment blinding was protected not only by non-disclosure of the state of the SCS device to the patients, but also by programming a current leak which prevented the patient from recognizing the sham condition through changes in recharging time

Blinding of outcome assessment *(detection bias)*	Low	
Incomplete outcome data *(attrition bias)*	Unclear, probably low	- 40 patients were eligible for randomization, and 33 had complete study data; the 7 patients who did not end up contributing outcome data included 4 who chose not to begin or to continue the study, 1 with lead breakage, 1 with battery exhaustion, and 1 withy pulse generator flipping - It is not likely that these withdrawals biased the results
Selective outcome reporting? *(reporting bias)*	Unclear, probably low	- There is no information on where the study was registered, and therefore the study protocol is not available - However, the results of the study, which did not support the initial study hypothesis that 5 KHz SCS would be effective, make it unlikely that selective outcome reporting occurred
Other bias		

Sponsorship if reported		
Study funding sources if reported	Medtronic funded the study but did not design or analyze the study results	
Possible conflicts of interest for study authors	No conflicts declared	
Notes:		

Comments by DOWC staff

- Although the study is provocative and raises important questions about the effectiveness of SCS, there are enough limitations to the study which do not support evidence that SCS is ineffective
- The study population had existing SCS for back pain with radiating leg pain, and is otherwise not described very well; for example, the duration of treatment was not described
- A flow diagram, which would identify the numbers of patients potentially eligible for the study, the number actually eligible, and the number who consented to participate, would normally be included in a high quality randomized trial, but was missing from this study
- In the discussion section, the authors attempt to estimate the mean benefit of HFSCS over sham SCS by averaging the proportions of responders in each treatment period; this is probably not a sound method of estimating the treatment effect, because of the large and dramatic size of the period effect
- It is also noteworthy that of the 8 patients who received and responded to sham SCS in the first treatment period, 4 said that they thought they had been given sham SCS, and still said that they were having better pain control than on conventional SCS; this phenomenon has no clear explanation, but does underscore the authors' statement that the nature of the therapy is not the dominant explanation of the therapeutic response to SCS
- There is a misprint in the discussion section on the left hand column of page 368, third paragraph from the bottom; "rehobase" is a misprint for "rheobase," which is related to membrane excitability as a possible explanation for why the subthreshold SCS of 5 KHz rather than 10 KHz did not appear to differ from sham SCS
- The authors designed the study with the hypothesis that 5KHz would produce analgesia without paresthesia, and this hypothesis is of little interest in light of the fact that 10KHz is the frequency of HFSCS which is generally used in clinical practice
- It is surprising that sham controlled trials of conventional or HFSCS have not been done and published; this would be technically possible and ethically defensible, since groups could have SCS implantation with immediate and deferred activation of the SCS device; the responses of the groups could be compared after implantation, and the deferred activation group could probably have the device activated after a short experimental treatment period without harm

Assessment by DOWC staff	
Overall assessment as suitability of evidence for the guideline ☐ High quality ☐ Adequate ☒ Inadequate	The study is not adequate to estimate the effectiveness or lack thereof of the 10 KHz SCS devices currently being used in clinical practice; however, it raises important questions which have not been adequately studied. Scientifically sound comparisons of true and sham SCS are lacking, whether of conventional or high-frequency SCS.

If inadequate, main reasons for recommending that the article not be cited as evidence	The dose was subthreshold, the study population was sparsely described, and the results would not apply to the treatment-naïve patients who would be considered for SCS implantation in a workers compensation guideline

Additional references if relevant
-