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Systematic review and meta-analysis of placebo/sham controlled randomised trials of spinal cord stimulation for neuropathic pain

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Abstract

The aims of this study review were to: systematically identify the current evidence base of randomised controlled trials (RCTs) of spinal cord stimulation (SCS) placebo (or 'sham') trials for neuropathic pain and (2) to undertake a meta-analysis to investigate the effectiveness of SCS when compared with a placebo comparator arm. Electronic databases were searched from inception until January 2019 for RCTs of SCS using a placebo/sham control. Searches identified eight eligible placebo-controlled randomised trials of SCS for neuropathic pain. Meta-analysis shows a statistically significant reduction in pain intensity during the active stimulation treatment periods compared to the control treatment periods; pooled mean difference -1.15 (95% confidence interval -1.75 to -0.55, p=0.001) on a 10-point scale. Exploratory study level subgroup analysis suggests a larger treatment effect in RCTs using a placebo control (defined as studies where the device was inactive and at least one of the study procedures was different between the arms) than a sham control (defined as all study procedures being equal between arms including SCS device behaviour). Our findings demonstrate limited evidence that SCS is effective in reducing pain intensity when compared to a placebo intervention. Our analyses suggest that the magnitude of treatment effect varies across trials and, in part, depends on the quality of patient blinding and minimisation of carryover effects. Improved reporting and further methodological research is needed into placebo and blinding approaches in SCS trials. Furthermore, we introduce a differentiation between placebo and sham concepts that may be generalisable to trials evaluating surgical or medical procedures.

Keywords: placebo; crossover randomised controlled trials; spinal cord stimulation; systematic review; meta-analysis

INTRODUCTION

Spinal cord stimulation (SCS) is a recognised option for the management of chronic neuropathic pain with randomised controlled trials (RCTs) performed to investigate its effectiveness for conditions such as failed back surgery syndrome (FBSS),[25] complex regional pain syndrome (CRPS)[21] and painful diabetic neuropathy.[6] Conventional medical management has however been the comparator most commonly used in RCTs to date evaluating SCS for neuropathic pain.

Reports have suggested that at least some part of pain relief observed at early stages of SCS therapy may be the result of a placebo effect with long-term follow-up revealing loss of efficacy for a proportion of participants when compared to the earlier primary endpoint.[9; 20; 22; 26; 34] It is widely accepted that use of placebo or sham controls in a clinical trial can reduce the unblinding bias (knowing the treatment received) of patients, clinicians, and researchers can result in non-specific treatment effects reported by patients. The literature suggests that factors relating to patient expectation of treatment success are central in the development of the placebo response; these are highly relevant in SCS use.[52]

In the last decade, several RCTs have evaluated SCS for neuropathic pain conditions when compared to a placebo arm. These RCTs have been possible due to the emergence of new sensation-free SCS modalities such as burst, high frequency or high density. Despite difficulties with blinding, conventional or paraesthesia producing SCS has been compared to placebo in a number of small studies with varied results, including the effects of placebo stimulation being similar to those of active treatments.[1; 37]

In our context ‘placebo trials’ are trials that specifically set out to select a comparator to ‘find out’ what might be the placebo effect of the active intervention e.g. RCT of low dose SCS vs traditional SCS (both groups get implant, etc). However, as we know, in this design there is high likelihood that patients will be aware of their allocation and therefore the design is effectively ‘open label’. Within this framework, we could therefore define ‘sham trials’ as a specific subgroup of placebo trials where there is the possibility to ‘fully blind’ patients, clinicians and researchers. In the neuromodulation setting this would need to be an active intervention vs comparator that is completely paraesthesia free e.g. RCT of HF10 vs no stimulation. Given the complexities in enabling a sham for a treatment such as SCS and for the purposes of this review, sham was defined as a control where all study procedures were equal between arms including implantable pulse generator (IPG) behaviour (i.e. need for recharging). Placebo was defined as a control where the IPG was inactive and at least one of

the study procedures was different between the arms (i.e. no IPG spontaneous discharge, i.e. built-in current leak), admitting overtly the possibility of unblinding.

We have recently conducted a systematic review that focused on the methodological facets of randomised placebo-controlled trials of SCS.[10] The aim of this systematic review was to investigate the effectiveness of SCS for patients with neuropathic pain when compared with a placebo comparator arm.

METHODS

The systematic review methods followed the general principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for conducting reviews in health care.[3] This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[31] The protocol for this review is registered on PROSPERO as CRD42018090412. The current review focuses on the effectiveness results of SCS placebo-controlled trials in patients with neuropathic pain.

Search strategy

Electronic databases MEDLINE, CENTRAL, EMBASE and WikiStim were initially searched from inception until February 2018 and updated on the 29th January 2019. The search strategies were designed using a combination of both indexing and free text terms with no restriction on language. The search strategy used for the MEDLINE database is presented in Supplementary material 1 of this manuscript (available at http://links.lww.com/PAIN/A868). The MEDLINE search strategy was adapted to enable similar searches of the other relevant electronic databases. The reference lists of relevant systematic reviews and eligible studies were hand-searched to identify further potentially relevant studies.

Study selection

The citations identified were assessed for inclusion in the review using a two stage process. First, two reviewers independently screened all the titles and abstracts identified by the electronic searches to identify the potentially relevant articles to be retrieved. Second, full-text copies of these studies were obtained and assessed independently by two reviewers for inclusion using the eligibility criteria outlined in Table 1. Any disagreements were resolved through discussion at each stage, and, if necessary, in consultation with a third reviewer.

[Insert Table 1 here]

Data extraction

A data extraction form was designed to enable data extraction relating to study author and year of publication, country where the study was conducted, study design, population, number of participants included in the analysis, intervention including frequency of stimulation (if reported), details on placebo or sham comparator, duration of placebo or sham, consideration of carryover effect and washout periods (for cross-over RCTs only) and efficacy outcomes assessed.

Data extraction was performed by one reviewer and checked for accuracy by a second reviewer. Any disagreements were resolved through discussion, and, if necessary, in consultation with a third reviewer.

Risk of bias assessment

We planned to assess risk of bias by using the revised Cochrane risk of bias tool (RoB 2.0) appropriate to the study design of the included trials. All the studies that met the eligibility criteria were cross-over trials. Therefore we used the RoB 2.0 specific for cross-over trials.[17] Risk of bias assessment of the included studies was undertaken by one reviewer and checked by a second reviewer. Any disagreements were resolved by discussion, and, if necessary, in consultation with a third reviewer.

Data synthesis

Our primary efficacy outcome was pain, reported on a validated scale such as visual analogue scale (VAS; 0 to 10 cm or 0 to 100 mm) or numeric rating scale (NRS; 0 to 10). To standardise to a single scale, we assumed that VAS (0 to 10 cm) and NRS (0 to 10) were equivalent and we converted VAS (0 to 100mm) by dividing pain scores by 10.

The measure of treatment effect for data synthesis was the mean difference and standard error of the mean difference between active stimulation and control, to be pooled via the generic inverse variance method of meta-analysis.[7]

For cross-over studies, we intended to extract in the first instance, the mean difference in pain scores between treatment periods and a measure of precision which takes account of the paired nature of the data.[14] If such data were not reported, or if we were concerned regarding carry-over effect across treatment periods, we would have extracted the mean pain

score and a measure of precision for the first treatment period only and treated these data as a parallel study in data synthesis.

Four included cross-over studies reported data only for the pain scores at the end of all treatment periods (i.e. the mean pain score and standard deviation of all participants during that treatment period). The results do not reflect the paired (correlated) nature of the data and if used in meta-analysis, would overestimate the variance of the pooled result. We received partial individual participant data for one study[37] and used these data to estimate a within-participant correlation value between treatment periods of 0.517. We were then able to calculate the mean difference and the standard error of the mean difference taking account of the correlated structure of the data using the formulae described in the Appendix of Elbourne et al.[14]

We were also able to extract individual participant data for 10 participants in one study[55] and used these data to estimate a within-participant correlation value between treatment periods of 0.963. We repeated all data synthesis using this correlation value to calculate the mean difference and the standard error of the mean difference. Numerical results of meta-analysis were similar and conclusions were unchanged (results not shown, available on request from corresponding author).

Three of the cross-over studies with mean difference and associated standard error adjusted for the paired design included more than one active treatment period and a sham or placebo [2] treatment period. To allow comparisons for each of the active treatments to the control treatment period to be included in meta-analysis without multiple counting of the control treatment period, we divided the number of participants included in the study by the number of comparisons when calculating the mean difference and associated standard error.

Assessment of heterogeneity and subgroup analysis

We assessed the level of heterogeneity present between trials by visual inspection of forest plots and formally according to the I^2 statistic (the percentage of variability between trials that is due to statistical heterogeneity). We anticipated that clinical heterogeneity would be present in analysis due to differences in study design and participant characteristics, therefore we performed a random-effects meta-analysis.[7]

We also performed subgroup analysis to further investigate statistical heterogeneity; we assessed the duration of treatment (subgroups of 1 to 4 weeks) and type of control (sham, placebo or other). Subgroup meta-analyses were also performed with random-effects due to anticipated heterogeneity between studies. We did not formally test for differences between

subgroups; rather we interpreted any visual differences in the pooled results across subgroups.

RESULTS

Study selection

The searches resulted in the identification of 1473 citations. After the removal of duplicate records, we identified 1309 potential citations. Following initial screening of titles and abstracts, 35 publications were considered to be potentially relevant and were retrieved to allow assessment of the full-text publication. After review of the full-text publications, 8 studies were included in the review.[1; 5; 24; 30; 37; 42; 49; 55] Twenty-seven studies were excluded at the full-text paper screening stage because the comparator was not a placebo or sham neurostimulation.[4; 6; 8; 9; 13; 18; 19; 21; 23; 25; 28; 32-35; 41; 43-48; 50; 51; 53; 54; 57] The PRISMA flow chart detailing the screening process for the review is shown in Figure 1.

[Insert Figure 1 here]

Characteristics of included studies

The characteristics of the eight included studies are summarised in Table 2. All the included studies were cross-over RCTs.[1; 5; 24; 30; 37; 42; 49; 55] Four studies restricted the participants to a specific condition such as FBSS[1; 37; 42] or CRPS.[24] Four studies included participants with a range of conditions.[5; 30; 49; 55]

The type of stimulation investigated in the studies included paraesthesia inducing, subthreshold, burst and high frequency SCS. Two studies included patients new to SCS (i.e. study was carried out immediately after implantation of the device).[1; 5] One of the studies with patients new to SCS involved a trial period conducted with an external IPG system via externalised extension wires. Participants who completed the 28-day period of external stimulation then underwent permanent implantation of the SCS device.[5] The remaining six studies included patients already receiving paraesthesia stimulation for at least four weeks before enrolment in the trial.[24; 30; 37; 42; 49; 55] The phases (i.e. different settings) in the cross-over RCTs ranged from two to five phases. The duration of each phase ranged from one week in three studies [5; 42; 55] to three weeks in one study.[1] One study included only a 12 hour interval before quantitative sensory testing (QST) assessment.[30] The duration of each cross-over phase was two weeks in three studies.[24; 37; 49] Four of the studies did not

consider a carryover effect or washout period between the different stimulation phases.[1; 5; 42; 55] In the studies that included a washout period, this period consisted of 12 hours,[30] two days [24] or a two week washout period with their own paraesthesia stimulation.[37; 49]

[Insert Table 2 here]

Risk of bias assessment

The summary of the risk of bias assessment is presented in Table 3. The full assessment for each included study is presented in Supplementary material 2 (available at http://links.lww.com/PAIN/A868). Four studies were judged to have some concerns for the randomisation domain, as no information was presented about how the sequence was generated or concealed.[5; 30; 49; 55] Although some studies included an intervention arm where patients would feel paraesthesias [24; 30] and therefore would not be blind to intervention, other studies [30; 42; 55] were judged to have a high risk of bias due to the possibility of a carryover effect (domain deviations from intended interventions). No information was presented in Tjepkema-Cloostermans et al[49] besides stating that the study was double-blind; therefore, it was judged as presenting some concerns of bias for the domain deviations from intended interventions. Four studies reported only information on patients that received the interventions and provided data at all assessment times (per protocol analysis) or did not report how many patients were initially randomised.[1; 30; 37; 55] Therefore, it was considered there were some concerns of bias for the missing outcome data domain. There were some concerns of bias for the measurement of the outcome domain in four studies as outcome assessors were aware of the intervention received by study participants or no information was provided.[5; 24; 30; 49] One study did not carry out statistical analysis appropriate for a cross-over design,[42] while another study did not report any analysis methods.[5] There were some concerns with selective reporting in the studies by Al-Kaisy et al,[1] De Ridder et al[5] and Kriek et al.[24] The numerical results were provided only for statistically significant results. This omission includes test for carryover effect which was not presented because it was not statistically significant.[1] It was considered that there were some concerns of bias regarding the selection of the reported result domain for these three studies. Overall bias of included studies ranged from some concerns to high risk of bias. None of the studies was considered to have a low risk of overall bias.

[Insert Table 3 here]

Outcomes of included studies

Pain outcomes, treatment satisfaction and patient stimulation preferences for all included studies are presented in Table 4.

Twelve comparisons of an active stimulation and control treatment period, including 155 participants from six cross-over studies could be pooled in meta-analysis to investigate the effect on pain intensity (Figure 2). We were unable to include any numerical results for two studies recruiting 30 participants within meta-analysis[5; 30] due to inadequate numerical data presented within the trial journal publications. Meta-analysis shows a statistically significant reduction in pain intensity (VAS 0 to 10cm or NRS 0 to 10) during the active stimulation treatment periods compared to the control treatment periods; pooled mean difference -1.15 (95% confidence interval [CI]: -1.75 to -0.55, p=0.001). There was a substantial amount of heterogeneity present between the comparisons (I^2 =65.8%).

[Insert Table 4 here]

[Insert Figure 2 here]

Subgroup analyses

We performed subgroup analysis to further investigate the duration of treatment (subgroups of 1 to 4 weeks) and type of control (sham, placebo or other) on the treatment effect.

Two studies had treatment periods of one week,[42; 55] two studies had treatment periods of two weeks,[37; 49] one study had treatment periods of three weeks[1] and one study had treatment periods of four weeks.[24] Subgroup analysis by duration of treatment shows no clear differences in treatment effect according to the duration of the stimulation and control treatment period (Figure 3). Duration of treatment is relevant particularly in respect of timing of pain data collection where some investigators have chosen to collect data only during the last three days of the period[1; 37] in order to minimise the impact of any carryover effect from the previous period.

[Insert Figure 3 here]

Two studies used a sham control,[1; 37] three studies used a placebo control[24; 42; 55] and one study used low amplitude burst stimulation as the control treatment (Figure 4).[49] Subgroup analysis by type of control shows that the treatment effect of stimulation compared

to control appears much larger in the studies using placebo control (pooled MD, -1.88, 95% CI -2.77 to -0.98) than the studies using sham control – IPG behaviour equal in all arms i.e. need for recharging (pooled MD, -0.34, 95% CI -1.04 to 0.36) and the study using low amplitude burst stimulation (MD -0.20, 95% CI -1.01 to 0.61). However, a substantial amount of heterogeneity remains between the studies using placebo control (I^2=65.2%).

[Insert Figure 4 here]

DISCUSSION

To our knowledge this is the first systematic review of randomised placebo ('sham') controlled trials of SCS for neuropathic pain. Our meta-analysis of six cross-over studies and a total of 155 participants has shown an average reduction in pain intensity (VAS 0 to 10cm or NRS 0 to 10) during the active stimulation treatment periods compared to the control treatment periods of -1.15 (95% CI: -1.75 to -0.55, p=0.001). The substantial statistical heterogeneity in effect across trials may be partly explained by the type of control. Exploratory subgroup analysis by type of control shows that the treatment effect of stimulation compared was larger in the studies using placebo control[24; 42; 55] than the studies using sham control.[1; 37]. We defined sham as a control when all study procedures were equal between arms including IPG behaviour (i.e. need for recharging) as opposed to placebo where the IPG was inactive and at least one of the study procedures was different between the arms (i.e. no spontaneous IPG discharge, i.e. no current leak). Presumably a sham control is more plausible to participants and would be associated with a smaller potential of unblinding particularly where the participants have prior experience with SCS. Accidental unblinding during the placebo phase might reduce the impact of the placebo arm and consequently inflate the effect of the active intervention. However, included studies were generally poorly reported and had methodological limitations related to quality of blinding and handling of carryover effects due to cross-over designs.

Despite limiting the scope of our review to subjects with neuropathic pain, we found a great deal of variation in pain conditions between the studies which varied from FBSS to general neuropathic pain with a range of conditions. Furthermore, the type of stimulation investigated included a wide range of modalities such as paraesthesia stimulation, subthreshold, burst and varying kilohertz frequencies up to 5880 Hz. In addition, the determination of the perception threshold in studies using subthreshold stimulation has been carried out in variable positions with a number of studies not reporting how the threshold was measured. Perceptual threshold

for conventional paraesthesia-based SCS varies by about 25% with simple postural changes, and this could easily lead to unblinding.[36] No study has yet evaluated the 10kHz frequency against a sham control.

All eight included studies employed a cross-over design with most including a number of treatment phases. In order to conduct a pairwise comparison of placebo versus various modes of stimulation the study populations were divided into pairwise comparisons and our statistical analysis was adjusted accordingly to take account of these different comparisons. The use of a cross-over design with a number of stimulation parameters and periods generates a risk of a carryover effect of active modes of stimulation spilling onto the placebo period. We note that, investigators employed various strategies to address the carryover issue such as including a washout period varying from 12 hours[30] to two weeks[49] or collecting outcomes at the end of the crossover period.[1; 37] However, we consider that despite these mitigating strategies estimating the impact of any carryover remains difficult to quantify. Indeed, in experimental animals, the duration of neuronal inhibition and pain relief by SCS often exceeds the stimulation period.[15; 29] These findings are consistent with clinical observations that analgesia not only occurs during the SCS, but also often outlasts the period of SCS.[16] In a study looking at intermittent versus continuous conventional SCS, Wolter and Winkelmüller suggest that in the majority of patients a clinically significant carryover effect is demonstrable during 90 minutes or less.[56] While clinical experience suggests the wash-out (as well as the wash-in) time is influenced both by the diagnosis and the stimulation mode, the fact remains that no reliable data on the duration of carryover effect are available. Therefore, it remains possible that the overall placebo effect in our meta-analysis has been increased by the carryover effect from active stimulation.

Only two studies examined the impact of the “period effect” or the order of the treatment introduction on outcomes. Perruchoud et al[37] concluded that the first treatment introduced produced the highest impact regardless of whether it was sham or active treatment; in contrast Al-Kaisy et al[1] found no period effect in their study.

Another factor which may impact the magnitude of the response to a placebo device in the studies is the plausibility of the sham control or inactive device. A sham/placebo control may be more plausible in de novo patients who lack familiarity with the functioning of an SCS device and have limited knowledge of the handheld controller and no clear estimate of the recharging period following a particular mode of stimulation. In contrast participants with long experience of SCS require a more robust placebo due to their ability to unmask a placebo device particularly where the recharging duration is drastically reduced.

Only two of the eight studies recruited de novo participants.[1; 5] The De Ridder study[5] was conducted entirely during the screening trial period where attitudes and expectations may differ from following an IPG implant.[40] Al-Kaisy et al used de novo patients as well as a robust placebo control including a controlled current leak from a rechargeable IPG; no handheld patient controller was issued throughout the study.[1] As such in this study two of the three frequencies tested produced pain relief that was not significantly different from placebo stimulation. In contrast, in the study by Kriek et al, the information on the placebo used is limited to "Programming placebo was performed with a 100-Hz stimulus to maintain an equal programming paradigm and sensation for the patient. However, the IPG was switched off immediately after 'programming' placebo stimulation and remained switched off during the coming 2- week test period."[24] Since the study tested high frequency as well as burst it is safe to assume that the participants were implanted with a rechargeable IPG. We however, found no reference in the manuscript to either the IPG being programmed to produce a current leak in the placebo phase nor could we find a clear indication of what arrangements were made to prevent accidental unblinding during the placebo phase based on a sudden reduction of need for recharging.

Apart from a single study that favoured placebo stimulation all other studies favoured the test stimulation mode. However, the pain intensity forest plot needs to be interpreted with caution, for while the Perruchoud et al study found no significant statistical or clinical difference between 5kHz stimulation and sham, it remains a fact that in the study 5kHz stimulation was better than placebo by a margin of 11% on the primary outcome measure.[37] Yet it may be argued that the electrodes were positioned to obtain the best overlapping paraesthesia rather than targeting Th9-Th10 level. In contrast the study of Tjepkema-Cloostermans found burst as well as low burst to be better than conventional stimulation.[49] Since the authors had initially conceived low burst as a placebo control these results are difficult to interpret.

Some of the studies included did not present a power calculation.[5; 30; 49] Considering the IMMPACT recommendation [11] of detection of ≥2.0 point pain difference in VAS/NRS between groups (and assuming a typical standard deviation of 2.5, 20% attrition and 90% power) a parallel group design study would need a total of ≥84 patients (42 per arm) and a cross-over design (with conservative assumption of no within correlation between pre and post VAS/NRS) would need a total of ≥24 patients. Four of the studies included were therefore not adequately powered at 90% level to detect differences in pain intensity between the groups. [5; 30; 42; 55]

Strengths and weaknesses

We believe this to be the first systematic review and meta-analysis of placebo-controlled trials of SCS in neuropathic pain. A focused eligibility criteria attempted to minimise the heterogeneity observed. The review process, including study identification, selection and data extraction, was carried out in line with PRISMA[31] and CRD guidance.[3] The review seeks to provide clarity and direction in reporting and methods in placebo (or sham) controlled trials in SCS, that may well have relevance to the broader field of neuromodulation trials.

The review cites a limited number of RCTs, none of which judged as having a low risk of bias. All of the studies employed a cross-over design in which each participant served as their own control, which can increase the statistical power of the study. Nonetheless, all of the included studies enrolled small sample sizes ranging from 10 to 40 participants, and while all the studies compared some form of SCS to sham, none used the same SCS comparator. The small study size, differing SCS modalities and differing control setups may explain the heterogeneity observed.

We were unable to include any numerical results for two studies recruiting 30 participants within meta-analysis[5; 30] due to inadequate numerical data provided in the publications. Furthermore, numerical results presented in four of the studies[1; 24; 42; 49] included in the meta-analysis were only suitable after our statistical adjustment for the within-patient correlation inherent to the cross-over design.

While we were aware of a number of RCTs comparing SCS to placebo in refractory angina,[12; 27; 58] we decided to limit the scope of our review to the trials recruiting participants with neuropathic pain due to the use of different outcome measures as well as the use of a parallel trial design in one of the studies.

CONCLUSION

In conclusion, the findings of this systematic review show that use of SCS leads to a decrease in pain intensity when compared to a placebo intervention. Nevertheless, exploratory sub-group suggest that the magnitude of treatment effect varies across trials and depends on methodological characteristics including quality of patient blinding and minimisation of carryover effects. No studies have been identified assessing SCS at 10kHz versus placebo. Further research is needed to evaluate the ‘true’ effect of SCS in decreasing pain intensity of patients with neuropathic pain. The differentiation between placebo and sham concepts

introduced in this paper merit further investigation in reviews and meta-analysis of trials evaluating surgical or medical procedures.

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Authorship statement: SE conceptualised the study. EM conducted the searches. RD, EM and SE screened the search results for eligibility. RD, SN and SE extracted the data. RD and SN conducted the risk of bias assessment. SN performed the data analysis. All authors contributed to drafts of the manuscript and approved the final version of the manuscript.

Supplemental video content

A video abstract associated with this article can be found at http://links.lww.com/PAIN/A869.

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FIGURE LEGENDS

Figure 1 PRISMA flow chart

Figure 2. Meta-analysis of pain intensity comparing active SCS stimulation to control
Note: Al-Kaisy 2018, Kriek 2017 and Schu 2014 included more than one active treatment period and a control treatment period. To allow each active treatment period to be compared to the control treatment in meta-analysis, we divided the number of participants included in the study by the number of comparisons when calculating the mean difference and associated standard error. In other words, eight participants contributed to each comparison in Al-Kaisy 2018, seven participants in Kriek 2017 and ten participants in Schu 2014.

Figure 3. Subgroup meta-analysis of pain intensity comparing active SCS stimulation to control, by duration of control (weeks)

Note: See footnote of Figure 2 for a description of the comparisons made from Al-Kaisy 2018, Kriek 2017 and Schu 2014

Figure 4. Subgroup meta-analysis of pain intensity comparing active SCS stimulation to control, by type of control

Note: See footnote of Figure 2 for a description of the comparisons made from Al-Kaisy 2018, Kriek 2017 and Schu 2014

Table 1 Eligibility criteria

Inclusion criteria (if all of the following met)	**Exclusion criteria (if any of the following met)**
1. Population comprised patients with neuropathic pain	1. Neurostimulation intervention other than SCS
2. Intervention was SCS (all stimulation protocols)	2. Comparator only included an alternative active stimulation protocol or a non-neurostimulation control
3. Comparator was placebo	3. Design/protocol paper, methodological paper, (systematic) review, meta-analysis, commentaries/editorial
4. Study design was an RCT (parallel or cross-over)	4. Insufficient information (e.g. study only available as a conference proceeding/abstract)

RCT=randomised controlled trial; SCS=spinal cord stimulation

Table 2 Characteristics of randomised controlled trials included in the systematic review

Author (year)	Study design*	Number in analysis and age ± SD	Intervention	Control	Phase and overall study duration	Carryover effect	Outcomes
Al-Kaisy (2018)[1]	Cross-over (3 active treatment periods and 1 sham treatment period)	24 (M=16; F=8) 47.9 years (range 33 to 60)	1200 Hz, 3030 Hz, and 5882 Hz	Sham (IPG turned on and discharging, but without electricity transmitted to the lead)	3 weeks (12 week cross-over with 4 phases/different settings)	No significant carryover (no numbers presented)	Pain (VAS 0 to 10cm) in back and leg, treatment satisfaction, PGIC
De Ridder (2013)[5]	Cross-over (2 active treatment periods and 1 placebo treatment period)	15 (M=4; F=11) 54 years (range 39 to 68)	Burst and paraesthesia stimulation (40 or 50 Hz)	Placebo (Burst stimulation was applied on the predefined electrode contacts until the patient experienced paraesthesia. Subsequently the stimulator intensity was decreased like in burst programming but continued until zero amplitude)	1 week (3 week cross-over with 3 phases/different settings)	No significant carryover (no numbers presented)	Pain (VAS 0 to 100mm) - limb, back and general pain. Pain vigilance and awareness questionnaire, treatment preference. Paraesthesias caused by the stimulation
Kriek (2017)[24]	Cross-over (4 active treatment periods and 1 placebo treatment period)	29 (M=4; F=25) 42.55 ± 12.83 years	40 Hz, 500 Hz, 1200 Hz and burst	Placebo (Programming was performed with a 100 Hz stimulus to maintain an equal programming paradigm and sensation for the patient. The IPG was switched off immediately after programming and remained switched off during the 2 week test period)	2 weeks (10 week cross-over with 5 phases/different settings)	Washout and no significant carryover (pain scores at the start of each period measured)	Pain (VAS 0 to 100mm), MPQ, Global Perceived Effect, patient preference of treatment setting
Meier (2015)[30]	Cross-over (1 active treatment period and 1 deactivated treatment period)	14 (M=5; F=9) 53 years (median)	Paraesthesia stimulation	Placebo (Device switched off)	12 hours (2 day cross-over with 2 phases/different settings)	Washout, carryover not measured but may have impacted on results	QST; mechanical thresholds, thermal thresholds, wind-up like pain, pain (NRS 0 to 10 cm), areas of painful symptoms
Perruchoud (2013)[37]	Cross-over (1 active treatment period and 1 sham treatment period)	33 (M=16; F=17) 54.2 ± 10.7	HF at 5 kHz	Sham (Programming occurred as for HF. The stimulator was switched off after completing programming and current leak programmed during the sham	2 weeks (8 week cross-over with 2 phases/different settings; before and after the first HF or sham phase there	Washout but highly significant period effect reported	PGIC, pain (VAS 0 to 100 mm), and quality of life (EQ-5D)

		years		periods)	was a 2 week period with paraesthesia SCS)		
Schu (2014)[42]	Cross-over (2 active treatment periods and 1 placebo treatment period)	20 (M=7; F=13) 58.6 ± 10.2 years	Subthreshold (500 Hz) and burst	Placebo (No stimulation was programmed; device switched off)	1 week (3 week cross-over with 3 phases/different settings)	No washout, stated that carryover may have impacted on the results	Pain (NRS, 0 to 10 cm), pain quality - SFMPQ, safety, pain related disability - ODI, patient stimulation preference
Tjepkema-Cloostermans (2016)[49]	Cross-over (1 active high stimulation treatment period and 1 control low stimulation treatment period)	40 (M=24; F=16) 58 years (range 41 to 73)	Burst	Low amplitude burst (0.1 mA bursts)	2 week (6 week cross-over with 2 phases/different settings; 2 week period with paraesthesia SCS between the 2 different settings)	Washout and no significant carryover (p value of period effect presented)	Pain (VAS 0 to 100mm), quality of life (MPQ), patient preference, proportion of patients with 30% extra pain reduction as compared with paraesthesia stimulation
Wolter (2012)[55]	Cross-over (1 active sub-threshold stimulation treatment period and 1 no stimulation treatment period)	10 (M=6; F=4) 54 ± 6.2 years	Subthreshold	Placebo (Device switched off)	1 week (2 week cross-over with 2 phases/different settings)	Not mentioned	Pain (NRS 0 to 10 cm), HADS, PDI and BDI

BDI=Beck depression inventory; F=female; HADS=hospital anxiety and depression score; HF=high frequency; IPG=implantable pulse generator; M=male; MPQ=McGill pain questionnaire; NRS=numerical rating scale; ODI=Oswestry disability index; PDI=pain disability index; PGIC=patient's global impression of change; QST=quantitative sensory testing; SD=standard deviation; SFMPQ=short-form McGill pain questionnaire; VAS=visual analogue scale

Table 3 Risk of bias assessment

Author (year)	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall Bias
Al-Kaisy (2018)[1]	Low	Low	Some concerns	Low	Some concerns	Some concerns
De Ridder (2013)[5]	Some concerns	Low	Low	Some concerns	Some concerns	Some concerns
Kriek (2017)[24]	Low	Low	Some concerns	Some concerns	Some concerns	Some concerns
Meier (2015)[30]	Some concerns	High	Some concerns	Some concerns	Low	High
Perruchoud (2013)[37]	Low	Low	Some concerns	Low	Low	Some concerns
Schu (2014)[42]	Low	High	Low	Low	Low	High
Tjepkema-Cloostermans (2016)[49]	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns
Wolter (2012)[55]	Some concerns	High	Some concerns	Low	Low	High

Table 4 Pain outcomes and treatment satisfaction / patient stimulation preferences

Author (year)	Pain intensity (VAS or NRS)	Other pain measures	Treatment satisfaction / patient stimulation preference
Al-Kaisy (2018)[1]	Mean low back pain scores were 4.83, 4.51, 4.57, and 3.22, for sham, 1200 Hz, 3030 Hz, and 5882 Hz, respectively, p=0.002 The mean leg pain scores were 3.06, 2.51, 2.37, 2.20, and 1.81, for baseline, sham, 1200 Hz, 3030 Hz, and 5882 Hz, respectively, p=0.367	PGIC - Statistically significant difference on subject scores among the frequency groups (p= 0.007), with more of those on sham reporting no change and more on 5882 Hz reporting considerable improvement	There were 63%, 63%, 75%, and 75% who were either very satisfied or somewhat satisfied with the therapy, in the sham, 1200 Hz, 3030 Hz, and 5882 Hz group, respectively, p=0.672 12 month open label phase - 29% of subjects elected to use 5882 Hz, 25% reverted to traditional stimulation, 21% and 12.5% chose either the 1200 Hz or the 3030 Hz setting, respectively, while 12.5% requested sham stimulation
De Ridder (2013)[5]	A comparison between placebo, paraesthesia inducing, and burst stimulation over back pain, limb pain, and general pain revealed an overall significant effect (F=4.31, p<0.05). Burst stimulation significantly differs from placebo stimulation for back pain, limb pain, and general pain, For back pain, no significant effect was obtained between paraesthesia inducing and placebo stimulation. However, analysis yielded a significant effect between paraesthesia inducing and placebo for limb pain and general pain	NR	After 4 weeks, patients were asked which stimulation design they preferred: all patients preferred burst mode. No patient indicated that paraesthesia inducing stimulation was unbearable
Kriek (2017)[24]	Mean pain scores were 39.83, 40.13, 42.89, 47.98, 63.74 for paraesthesia inducing, 500 Hz, 1200 Hz, burst and placebo, respectively, p<0.001	MPQ – average pain scores were 4.70, 5.10, 5.31, 5.66, 7.07 for paraesthesia inducing, 500 Hz, 1200 Hz, burst and placebo, respectively, p<0.001	14 (48%) preferred the paraesthesia inducing (40 Hz) frequency stimulation and 15 (52%) preferred one of the non-standard stimulation modalities
Meier (2015)[30]	Median pain scores were similar during SCS activated (4.5 [IQR, 3 to 6]) and SCS deactivated (4.5 [IQR, 3 to 8])	Wind-up like pain - no statistical differences were found between the QST sessions	NR
Perruchoud (2013)[37]	Adjusted for baseline pain VAS (under normal stimulation), the mean pain VAS on sham was 4.26 vs. 4.35 on HF; the difference (HF minus sham) =-0.09 (95% CI, -0.68 to 0.86; p=0.82).	PGIC - There was a statistically significant "period effect," whereby 51.5% (17/33) of patients improved at visit 3 and only 21.2% (7/33) at visit 5, irrespective of treatment received (mean difference in proportions = 30.3%; 9–51%; p=0.006)	The overall proportion of patients responding to HF stimulation was 42.4% (14/33 patients) vs. 30.3% (10/33 patients) in the sham condition

Schu (2014)[42]	Mean pain scores were 5.6, 7.1, 4.7, 8.3 for 500 Hz, burst and placebo, respectively, $F_{2,57}$=19.07, p<0.0001	SFMPQ – mean scores were 25, 28.6, 19.5, 33.5 for paraesthesia stimulation, 500 Hz, burst and placebo, respectively, $F_{2,57}$=8.64, p=0.0005)	Burst stimulation was preferred by 16 patients (80%), 500-Hz stimulation by two patients (10%), and paraesthesia stimulation (baseline) by two patients (10%). None of the patients preferred placebo stimulation
Tjepkema-Cloostermans (2016)[49]	Mean pain scores were 52, 42, 40 for paraesthesia stimulation, low burst and high burst, respectively, p=0.012	PRI – mean scores were 20.4, 19.7, 18 for paraesthesia stimulation, low burst and high burst, respectively, p=0.34	Eleven patients preferred paraesthesia stimulation, 15 preferred high amplitude burst and 14 preferred low amplitude burst SCS
Wolter (2012)[55]	Mean pain scores were 3.6, 5.6, 6.4 for paraesthesia stimulation, subthreshold and no stimulation, respectively. Paraesthesia inducing vs subthreshold, p=0.0059; subthreshold vs no stimulation, p= 0.0020; paraesthesia inducing vs no stimulation, p=0.0020	PDI -mean scores ranged from 3.8 (item 'vitally indispensable activities') to 6.3 (item 'professional activities'); scores not presented by type of stimulation	NR

HF=high frequency; IQR=interquartile range; MPQ=McGill pain questionnaire; NR=not reported; NRS=numerical rating scale; QST=quantitative sensory testing; PDI=pain disability index; PGIC=patient's global impression of change; PRI=pain rating index; QST=quantitative sensory testing; SCS=spinal cord stimulation; SFMPQ=short-form McGill pain questionnaire VAS=visual analogue scale