Advances in neurostimulation for chronic pain disorders

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Definitive treatment or 'cure' for chronic pain disorders continues to be elusive. The field of neurostimulation has seen numerous advances in recent years, ranging from new stimulation waveforms (e.g. burst, high frequency, high density) to new neural target areas (e.g. dorsal root ganglion [DRG]) always with the aim to decrease pain and improve patients' quality of life. Since the first randomised controlled trial (RCT) of spinal cord stimulation (SCS) in 2000,[1] there has been ongoing improvement in the quality of evidence on the use of neurostimulation for different chronic pain disorders.

Deer and colleagues carried out comprehensive systematic reviews to assess the quality of the evidence on SCS,[2] brain neurostimulation,[3] DRG stimulation,[4] and peripheral nerve stimulation (PNS) [5] for the treatment of pain. A total of 23 RCTs (i.e. SCS n=6; deep brain stimulation [DBS] n=2; DRG n=1; PNS n=14) were identified in the field of neurostimulation since the beginning of the millennium. The authors employed different tools to assess the risk of bias of the studies and grading of the body of evidence, with consideration of the risk of bias. However, the tools used fail to judge potential inconsistency of results and do not allow grading of evidence according to treatment outcomes evaluated in the included studies. Future systematic reviews should consider using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to rate the quality of the evidence and strength of recommendations for neurostimulation interventions.[6] The key points made in the reviews would benefit from appraisal using the GRADE system (i.e. strength of recommendation considering the population, intervention, comparator and outcome).

The authors followed the statement of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) for their reviews. One of the items to consider according to PRISMA is the availability of a review protocol or registration of the review. This is of

particular importance given that the type of studies considered for inclusion across the four reviews varied considerably. This is understandable as the evidence available may differ for each technology (e.g. limited RCT evidence available for DRG). The eligibility criteria were particularly restrictive for the SCS review. It is unclear as to why some RCTs were excluded. According to the study eligibility section, studies should have a minimum duration of follow-up of three months, however in the discussion the authors state that some RCTs did not meet criteria for inclusion because of less than six months duration or small sample size. A minimum sample size was not part of the eligibility criteria disclosed. A pre-defined protocol should prevent these discrepancies. Transparency and potential for reproducibility of research is paramount also for systematic reviews.

One of the main sources of bias in RCTs of SCS has been the inability to blind participants to treatment allocation. The development of sensation-free stimulation has facilitated the design of RCTs with sham controls and participant, treatment provider and outcome assessors blind to treatment assignment.[7,8] To date these have been small studies, many with crossover design. A recent systematic review and meta-analysis identified eight crossover RCTs with a placebo/ sham control.[7] None of these studies met the eligibility criteria for the review by Deer and colleagues.[2] Grading of the evidence might have been affected by inclusion of these studies due to inconsistency of the results reported across the larger body of evidence.[7,8]

Painful diabetic neuropathy is a chronic pain condition that would also meet the definition by Deer et al of intractable or refractory pain. The effectiveness of SCS for painful diabetic neuropathy has been the subject of two RCTs with follow-up of at least six months.[9,10] The reason for not considering the use of SCS for painful diabetic neuropathy and thus exclusion of these two RCTs is unclear.

While the earlier SCS studies in this analysis used other treatments as controls, reporting superiority of the former over the latter, the most recent studies have compared novel waveforms and devices with their older counterparts.[11-13] Reported superiority of new over older technology has been offset by a report that when crossover data were collected, the older technology was superior in a substantial fraction of patients.[11] To the extent that one device should be capable of delivering both waveforms, from the clinical perspective these studies model a false or irrelevant choice. We look forward to studies which compare multimodal SCS with medical and surgical alternatives and which accordingly are more relevant to clinical practice.

Most SCS studies [9,12,13] have recruited participants with either failed back surgery syndrome or more recently chronic low back and leg pain.[12,13] These are highly heterogenous populations with complaints ranging from pure nociceptive to pure neuropathic pains.[16,17] The heterogeneity of the target population added to strict exclusion criteria casts some doubt on the generalisability of some of the study findings to daily practice.

Industry sponsored SCS trials have strengthened and enriched the evidence; however, transparent reporting of the methods is particularly relevant in this field to ensure this potential bias is minimised. A non-industry sponsored RCT [17] has reported noticeably inferior outcomes despite recruiting a similar population. TRIAL-STIM, a non-industry sponsored RCT has now been completed and results await publication.[18] MODULATE-LBP, is an ongoing double-blind, randomised, sham-controlled non-industry sponsored trial evaluating 10 kHz SCS to sham.[19] The results of these trials will undoubtedly further inform subsequent grading of evidence in the field of SCS. The limited number of studies reporting on DRG stimulation prevents an adequate critical appraisal of its risk benefit to patients in the long term.

Recent RCTs of SCS with technical refinements including new waveforms have reported a growing proportion of patients experiencing pain reduction levels ≥80%.[12,13] Although not representing a 'cure', such levels of pain reduction if associated with improvements in function and quality of life are certainly a great improvement in the outcomes of the earlier trials of neurostimulation.

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