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Holistic Treatment Response: An International Expert Panel Definition and Criteria for a New Paradigm in the Assessment of Clinical Outcomes of Spinal Cord Stimulation

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ABSTRACT

Background: Treatment response to spinal cord stimulation (SCS) is focused on the magnitude of effects on pain intensity. However, chronic pain is a multidimensional condition that may affect individuals in different ways and as such it seems reductionist to evaluate treatment response based solely on a unidimensional measure such as pain intensity.

Aim: The aim of this article is to add to a framework started by IMMPACT for assessing the wider health impact of treatment with SCS for people with chronic pain, a "holistic treatment response".

Discussion: Several aspects need consideration in the assessment of a holistic treatment response. SCS device data and how it relates to patient outcomes, is essential to improve the understanding of the different types of SCS, improve patient selection, long-term clinical outcomes, and reproducibility of findings. The outcomes to include in the evaluation of a holistic treatment response need to consider clinical relevance for patients and clinicians. Assessment of the holistic response combines two key concepts of patient assessment: (1) patients level of baseline (pre-treatment) unmet need across a range of health domains; (2) demonstration of patient-relevant improvements in these health domains with treatment. The minimal clinical important difference (MCID) is an established approach to reflect changes after a clinical intervention that are meaningful for the patient and can be used to identify treatment response to each individual domain. A holistic treatment response needs to account for MCIDs in all domains of importance for which the patient presents dysfunctional scores pre-treatment. The number of domains included in a holistic treatment response may vary and should be considered on an individual basis. Physiologic confirmation of therapy delivery and utilisation should be included as part of the evaluation of a holistic treatment response and is essential to advance the field of SCS and increase transparency and reproducibility of the findings.

Keywords: Chronic pain, holistic treatment response, minimal clinical important difference, physiologic confirmation of therapy, spinal cord stimulation

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INTRODUCTION

The International Association for the Study of Pain (IASP) has revised the definition of pain to "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage," with six accompanying descriptors and the etymology of the word "pain."[1] One of the descriptors states that "pain is always a personal experience that is influenced to varying degrees by biological, psychological, and social factors,"[1] and as such may affect individuals in different ways. The revised IASP definition has been implemented by the World Health Organization in the International Classification of Diseases update that came into effect on January 1, 2022.[2]

Chronic pain has been further defined by IASP as pain that persists or recurs for longer than three months.[3] Both chronic primary pain (eg, complex regional pain syndrome, nonspecific low back pain)[4] and chronic secondary pain syndromes (eg, cancer-related pain, neuropathic pain)[3] may interfere with activities of daily life, cause emotional distress, and negatively affect health-related quality of life (HRQoL). Although multiple outcomes are commonly assessed in clinical trials of chronic pain interventions, the design and interpretation of the results of such trials are usually focused on the magnitude of treatment effects on pain intensity. Because the experience of pain is multidimensional and personal, it seems reductionist to evaluate treatment response of a multidimensional condition solely on the basis of a unidimensional measure such as change in pain intensity. Indeed, it has been observed that pain intensity did not have independent predictive value on HRQoL score in patients with chronic pain.[5]

Spinal cord stimulation (SCS) is a recommended intervention for the management of both refractory chronic primary and secondary pain syndromes.[6–12] As neurostimulation technology advances and substantial reductions in pain intensity are more commonly observed in clinical trials with long-term follow-ups,[13–15] the pursuit of a holistic treatment response beyond pain intensity alone has gained increased interest.[16–19] Assessment of the comprehensive impact of a pain therapy requires consideration of multiple domains affected by and contributing to the chronic pain condition.

In this article, we extend the current Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations[20,21] to propose a framework for assessing the wider health impact of treatment with SCS for people with chronic pain, a "holistic treatment response."

Spinal Cord Stimulation

Understanding the modes of action and how these relate to treatment response is paramount to understanding the potential causes of unexplained loss of efficacy in the long-term use of SCS. Questions of the effectiveness of SCS have been raised because the initial short-term benefits are sometimes not observed in the long term.[22,23] A dose-response relationship is a central parameter for the evaluation of pharmacologic interventions[24,25] and commonly considered for psychologic interventions.[26,27] A dose-response effect should also be a central concept in SCS therapy. Assessment and reporting of the nature of this dose-response effect are important to understand the treatment effects and increase the transparency and reproducibility of the findings in SCS studies. Concepts of neural dosing expressed as charge per pulse (amplitude [mA] x pulse width [ms]) or charge per second (amplitude [mA] x frequency [Hz] x pulse width [ms]),[28] consequent evidence of neural response (measured through evoked compound action potentials [ECAPs, mV][29] or other mechanisms), and relationship to clinical outcomes have been proposed as potential methods to evaluate a dose-response effect (Table 1). When it is not possible to provide SCS measurements such as charge per pulse or second and neural response, at a minimum, the programmed parameters and utilization should be reported with clinical outcomes for physicians to evaluate the true effectiveness of a therapy. Although historically, these data have been difficult to capture, ideally, all SCS therapies should provide real-time, objective assessment in vivo of a physiologic response to the applied neural dose. This would allow to progress our understanding of the different types of SCS and improve patient selection, long-term clinical outcomes, and reproducibility of these clinical outcomes.

Composite Outcomes

A common approach to integrating consideration of wider health impacts of interventions and multiple outcomes in clinical trials is the use of composite outcomes. A composite outcome is a combination of at least two outcomes into a single measure to evaluate the broader impact of health interventions. A key consideration in the design of a composite outcome is that it should reflect both the key domains of unmet health of the condition or health problem being investigated and the response to treatment on these domains. The components that contribute to a composite outcome should be measurable events that can be sensibly added together as being relevant aspects of the condition being evaluated (for the patient or the health care provider, or both).[34] A systematic review of the use of composite outcomes in clinical trials concluded that its use is particularly problematic when the components are inappropriately combined, inconsistently defined, and inadequately reported.[35]

Composite outcomes should therefore incorporate multiple core domains that present a holistic view of the patient's health condition. This is particularly important for the clinician to consider while evaluating the treatment response of any interventional therapy. Learnings from previous research, combined with both patient and clinician input, are imperative to ensure that a composite outcome is clinically relevant.[36] Core outcome measures for assessment of important domains for patients with chronic pain have been recommended by IMMPACT[20,21] and corroborated by an IMMPACT survey of patients with chronic pain (Table 2).[38] Recently, improvement in function and decrease in pain intensity were most often reported as important goals specific to neuromodulation interventions by health care providers, with an increase in HRQoL most often stated as the definition of success of neuromodulation.[37]

Holistic Response Framework

In general terms, "holistic" indicates that a system and its properties are analyzed as a whole, in a global and integrated way, because from this point of view, its operation can only be understood in this way and not only as the simple sum of its component parts. A holistic response is plausible with SCS given the affective components of pain,[40,41] and improvements observed in emotional and sleep domains may be related with supraspinal and suprasegmental activation with SCS.[42] Definition of a holistic treatment response should consider the response in domains judged as important by patients,[38,39] health care providers,[37] and best practice recommendations.[20,21] Assessment of the holistic response combines two key concepts of patient assessment: 1) the patient's level of baseline (pretreatment) unmet need across a range of health domains; and 2) indication of patient-relevant improvements in these health domains with treatment.

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Table 1. Parameters and Proposed Mode of Action for the Different Types of SCS.

Type of SCS	Programming type	Programming inputs	Pulse width[21]	Amplitude[21]	Charge per pulse	Primary mode of action*	Physiologic response measured?
Open-loop	Low frequency	Patient subjective report	100–500 ms	1–10 mA	0.1–5 mC	Activation of Aβ fibers in the dorsal column that activate inhibitory interneurons in the spinal dorsal horn. These interneurons modulate release of inhibitory neurotransmitter GABA[30]	No
	Fast-acting subperception**	Patient subjective report	160–260 ms	1–10 mA*	0.16–2.6 mC	Surround inhibition through electrical activation of Aβ fibers or dorsal columns leading to synaptic activation of inhibitory interneurons[31]	No
	High frequency	Patient subjective report	30–150 ms	1–5 mA	0.03–0.75 mC	Unclear; working hypotheses are that stimulation of the dorsal column 1) may induce a depolarization block, thereby preventing the propagation of action potentials, 2) may induce desynchronization that can result in pseudospontaneous or stochastic neuronal activity in the spinal "gate," or 3) may induce temporal summation in which multiple impulses induce neuronal activation within a certain timeframe[30]	No
	High charge	Patient subjective report	150–800 ms	1–5 mA	0.15–4 mC	Low charge per pulse unlikely to activate fibers or neurons High charge per second may modulate dorsal column fibers[28]	No
	Burst	Patient subjective report	500 ms 20–1000 ms	1–5 mA 1–5 mA	0.5–2.5 mC 0.02–5 mC	Activation of medial and lateral spinothalamic tract includes activation of GABAergic interneurons in the spinal dorsal horn[30]	No

(Continued)

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Table 1. *Continued*

Type of SCS	Programming type	Programming inputs	Pulse width[21]	Amplitude[21]	Charge per pulse	Primary mode of action*	Physiologic response measured?
Closed-loop	ECAP-guided	Objective measurement of physiologic response (ECAPs) refined with patient subjective report	100–450 ms	Automatically adjusted for every pulse usually within 1–10 mA	0.1–4.5 mC	Activation of myelinated fibers in the dorsal column confirmed by conduction velocity measurements, which activate inhibitory interneurons in the spinal dorsal horn. Hypothesized that these interneurons modulate release of inhibitory neurotransmitter GABA	Yes. ECAPs are measured and recorded from the epidural space via the implanted electrode. Physiologic dose that produced clinical effect = ECAP 22.5 mV; therapy utilization 88%[13]

GABA, γ-amino butyric acid.
*In addition to the primary mode of action, it is hypothesized that similarly for all types of subperception stimulation, the constant electrical field along the rostrocaudal plane selectively engages the synaptic terminals of rostrocaudally oriented inhibitory interneurons in the superficial dorsal horn.[32,33]
**Depends on the patient perception threshold, necessary to be at 30% of the perception threshold.

Assessment of Patient Baseline Unmet Health Need

Treatment response should consider whether the baseline scores were indicative of dysfunction for the different domains. Inclusion criteria for trials specify scores required for some of the domains evaluated, generally for the primary outcome (eg, a baseline pain score of at least 60 mm in a visual analog scale). However, baseline scores for some of the secondary outcomes are not usually considered in the eligibility criteria. As such, and because the experience of pain may not affect all individuals in the same manner, it is plausible that some patients may not experience dysfunction in some domains. For example, some patients with chronic pain may not experience sleep or emotional dysfunction. In those instances, clinical improvements in nondysfunctional domains may not be observed, not because of inadequate treatment response but because the patient did not experience dysfunction in that domain before initiation of the treatment. Dysfunction can be established through consideration of normative values for each specific domain (Table 3).

Assessment of Patient Treatment Effect

For patient-reported health outcomes, minimal clinical important difference (MCID) is an established approach to reflect changes after a clinical intervention that are meaningful for the patient.[51] MCIDs commonly used to evaluate treatment response based on different outcomes are presented in Table 3. Different MCIDs may have been proposed for the same outcome. A recent study specific to patients with SCS proposed an MCID for pain intensity between 0.9 and 2.7.[52] An MCID of 2 points or ≥ 30% pain reduction may be more appropriate because it has been previously suggested that a 1-point change or percentage changes of approximately 15% to 20% may represent minimally useful but perhaps not very impactful decreases of chronic pain intensity.[43]

Commonly used outcome measures may assess more than one domain within the questionnaire. An example includes the PROMIS-29 tool, which enables a more rounded assessment of the status of a patient with chronic pain but also individual scores for subscales that represent different domains. When available, MCIDs based on the population of interest and for each specific domain of an instrument should be used. An MCID of 2 points has been suggested for the pain intensity, pain interference, and physical function domains of the PROMIS-29.[53] A review has observed that the MCID for PROMIS-29 domains can range from 0.1 to 12.7 points but considered it reasonable to assume an MCID value from 2 to 6 points.[54] An MCID of 5 points for the PROMIS-29 domains (with the exception of pain intensity) has been recommended in a recent study of patients with chronic low back pain.[55] When different MCIDs have been proposed, sensitivity analysis should account for alternative plausible MCIDs.

Interpretation of a Holistic Treatment Response

Different domains can be assessed with the use of specific outcome measures or questionnaires that encompass those domains of interest. Moreover, treatment response should only be evaluated for domains in which patients experience dysfunction. Consideration should also be given to deterioration of a domain within normative values at baseline to dysfunctional values at follow-up in response to the intervention. The number of domains included in a holistic treatment response may vary and should be considered on an individual basis. For example, a patient with dysfunctional levels for four domains would be considered a holistic responder if obtaining MCIDs for those four outcomes. When dysfunctional levels are observed in five domains but MCIDs

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Table 2. Outcomes for Assessment of Each Domain and Importance Reported by Health Care Providers and Patients.

Domain	IMMPACT recommended outcomes[20,21]	Health care providers[37]	Patients[38,39]
Pain intensity	NRS, VAS	√	√
Physical functioning	ODI, BPI, RMDQ, WOMAC function	√	√
Emotional functioning	BDI, HADS, POMS		√
Sleep and fatigue	MOS sleep scale, PSQI	√	√
HRQoL	EQ-5D, SF-36	√	√

BDI, Beck Depression Inventory; BPI, Brief Pain Inventory; HADS, Hospital Anxiety and Depression Scale; MOS, Medical Outcomes Study; NRS, numerical rating scale; ODI, Oswestry Disability Index; POMS, Profile of Mood States; PSQI, Pittsburgh Sleep Quality Index; RMDQ, Roland-Morris Disability Questionnaire; SF-36, 36-Item Short Form Survey; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Arthritis Index.

only obtained for four outcomes, the patient would be considered a multimodal responder but not a holistic responder (Fig. 1). Mean of MCIDs achieved for individual domains and mean of the sum of MCIDs across the different domains may provide valuable information regarding the magnitude of treatment response in the assessment of the wider health impact of the intervention. Physiologic confirmation of therapy delivery and utilization should be included as part of the evaluation of a holistic treatment response.

CONCLUSIONS

It is increasingly recognized that for new treatments to be considered innovative and useful for patients and health care systems, they need to show evidence of their benefit in a broader range of domains of health rather than in a specific symptom alone. This is particularly the case in the field of pain, in which the focus of treatment success and clinical trial design and assessment has been a reduction in pain intensity. In this article, building on the IMMPACT outcome framework, we propose assessing the wider health impact of treatments for people with chronic pain—"holistic treatment response." The field of chronic pain and SCS is moving beyond the limited validity of a pain intensity score toward an advanced realistic paradigm of evaluating the holistic response of a treatment option that aligns with the biopsychosocial complexity of the chronic pain condition. The aim is to support the individual patient to obtain improvements in all aspects of their health affected by their chronic pain instead of the no longer sufficient subjective assessment of decrease in pain intensity. There are several concurrent ongoing efforts to develop new composite and holistic outcome assessments in the field of chronic pain and neurostimulation. Although new developments will undoubtedly support current knowledge and advance this field, it is important that new composite outcomes are at a minimum characterized by 1) ease of use in routine clinical practice and 2) components of the composite consider core domains of relevance, and are informed by patients, clinicians, and best practice recommendations. A holistic treatment response needs to account for MCIDs in all domains of importance for which the patient presents dysfunctional scores before the start of the intervention. Furthermore, sensitivity analysis should be presented to consider different plausible ranges for MCIDs. Finally, establishment of an objective physiologic-based dose-response effect is essential to advance the field of SCS and increase transparency and reproducibility of the findings. At a minimum, the programmed parameters and therapy utilization should be reported.

Authorship Statements

All authors contributed to drafts and approved the final version of the manuscript.

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Table 3. Example of Minimal Clinical Important Differences and Population Normative Values.

Outcome	MCID	Source	Normative value	Source
NRS, VAS	Moderately important ≥ 30% Substantial ≥ 50%	IMMPACT[43]	< 60 mm (or as specified in trial eligibility criterion)	Clinical trial
ODI	≥ 10 decrease ≥ 15 decrease	Ostelo[44] Fairbank[45]	< 10.19 (normative value)	Fairbank[45]
POMS	≥ 10 to ≥ 15 decrease	IMMPACT[43]	17.7 (US adult normative value)	McNair[46]
PSQI	≥ 3 decrease	Buysse[47]	6.3 (US community sample)	Buysse[48]
EQ-5D	≥ 0.074 increase	Walters[49]	0.830 (US normative value for 55 to 64 y old)	EuroQol group[50]

NRS, numerical rating scale; ODI, Oswestry Disability Index; POMS, Profile of Mood States; PSQI, Pittsburgh Sleep Quality Index; RCT, randomized controlled trial; VAS, visual analogue scale.

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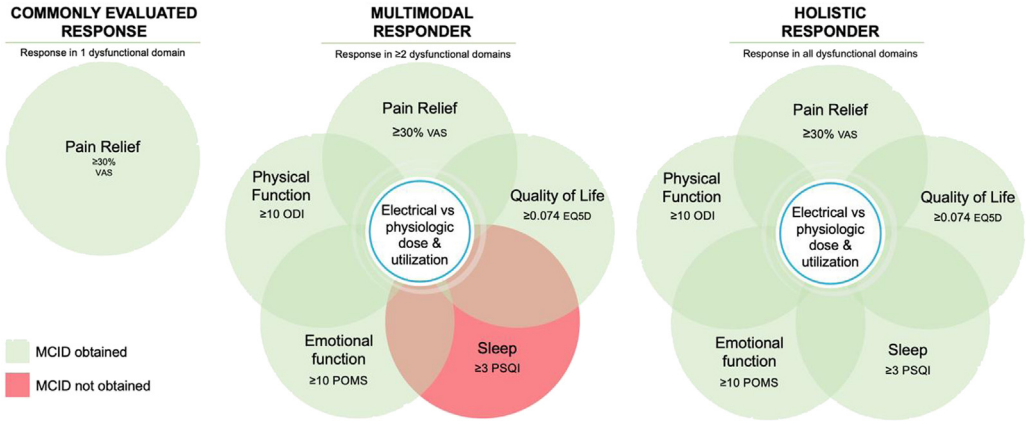

Figure 1. Illustrative example of different types of treatment response when multiple domains are considered (assumes patients would have dysfunctional baseline scores for the five domains). ODI, Oswestry Disability Index; POMS, Profile of Mood States; PSQI, Pittsburgh Sleep Quality Index; VAS, visual analogue scale. [Color figure can be viewed at www.neuromodulationjournal.org]

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