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Validation of a holistic composite outcome measure for the evaluation of chronic pain interventions

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Abstract

Introduction: Chronic pain is a personal experience influenced by multiple biopsychosocial factors. Using a pain intensity measure alone to assess the effectiveness of a chronic pain intervention fails to fully evaluate its impact on the multifaceted chronic pain experience. The holistic minimal clinically important difference (MCID) is a composite outcome developed to provide a comprehensive assessment of chronic pain in response to intervention, across 5 outcome domains: pain intensity, health-related quality of life, sleep quality, physical, and emotional function. To focus on domains where the individual need is greatest, the holistic MCID reflects the cumulative MCID averaged over only the domains where subjects were impaired preintervention.

Objectives: To assess the internal and construct validity of the Holistic MCID score to inform its future use as an evidence-based tool.

Methods: This validation study was undertaken using data from the EVOKE trial with 111 patients up to 24-month follow-up. Internal consistency of the holistic MCID was assessed using Cronbach alpha statistic and dimensional exploration using principal component analysis.

Results: The holistic MCID measure demonstrated strong internal consistency with Cronbach alpha >0.7 at all follow-ups. Principal component analysis showed one overarching holistic dimension to be present in the composite. Construct validity was demonstrated by an increase in the holistic MCID score being associated with both increased Patients' Global Impression of Change, EuroQol visual analogue scale score, and each of the outcome domains in a "leave-one-out" analysis (all $P < 0.001$).

Conclusion: The holistic MCID provides a valid measure for the comprehensive, personalized assessment of response after a chronic pain intervention. The validity of the holistic MCID requires further confirmation in other chronic pain populations and with different interventions.

Keywords: Chronic pain, Construct validity, Holistic composite outcome measure, Internal consistency, Minimal clinical important difference, Pain measurement

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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1. Introduction

Chronic pain is a common, complex, and distressing condition that is difficult to quantify and experienced uniquely by each individual. The International Association for the Study of Pain (IASP) definition states that "pain is always a personal experience that is influenced to varying degrees by biological, psychological, and social factors."[47] Despite wide recognition of chronic pain as a complex biopsychosocial phenomenon, clinical trials of interventions for chronic pain etiologies focus primarily on pain intensity alone and regulatory agencies focus on pain intensity when deciding whether to approve therapies for use. The most commonly used methods for measuring pain intensity are visual analogue scale (VAS) and numeric rating scale (NRS), both of which are limited to subjective interpretations of pain that typically fail to adequately reflect the wider biopsychosocial chronic pain experience and how it affects an individual's overall health.[13] This shortcoming has led scientists and practitioners, alike, to search for different means of evaluating pain that takes into account more aspects of well-being, thus allowing for a more accurate evaluation of the pain experience.

A composite outcome combines 2 or more outcomes into a single measure to evaluate the broader impact of health interventions.[11] A holistic composite measure for chronic pain needs to capture the various outcome domains that reflect both the unmet health need of the condition and the response to intervention. These outcome domains should reflect their importance to patients with chronic pain,[25,54] health care providers,[24] and also consider current core outcome recommendations.[15,32]

An international expert panel developed the holistic minimal clinically important difference (MCID) outcome as a comprehensive composite outcome measure based on the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) guidance for outcome assessment in chronic pain and US Food and Drug Administration (FDA) recommendations for composite outcomes.[20] The holistic MCID uses recommended and validated patient-reported outcome measures (PROMs), assesses normative population values to determine unmet health needs, and evaluates treatment response based on changes that are meaningful to patients.[35] The holistic MCID measure comprises the 5 domains of pain intensity, physical function, health-related quality of life (HRQoL), emotional function, and sleep quality. The holistic MCID score reflects the cumulative MCID score after intervention, averaged over only the domains where subjects were impaired preintervention. We have demonstrated the application of the holistic MCID score concept in the setting of a clinical trial.[30]

The validity of composite outcome measures for chronic pain has not been frequently assessed or reported. The objective of this study was to assess the internal and construct validity of the holistic MCID score to inform the future use of the holistic MCID score as an evidence-based tool.

2. Methods

2.1. Study population

The EVOKE [NCT02924129] trial was a participant, investigator, and outcome assessor-blinded, parallel-arm study. The study was conducted at 13 US centers and randomized 134 participants with chronic, intractable back and leg pain to evoked compound action potentials (ECAP)-controlled closed-loop spinal cord stimulation (SCS) or open-loop SCS. Details of the study design and outcomes are reported elsewhere.[34,38–40] The study was conducted in compliance with ethical and regulatory guidelines and was approved by local ethics committees prior to subject enrollment. The current study utilizes individual patient EVOKE trial data for those 111 participants who provided complete outcome data at a follow-up to 24-month post-implant (n for participants at each time point is detailed in **Table 1**).

2.2. Basis of the holistic minimal clinically important difference score

The development of the holistic composite outcome and holistic treatment response has been previously described[35] and was based on 5 key principles:

2.2.1. Components of the holistic composite outcome

The holistic MCID outcome comprises 5 domains of significance to a chronic pain population: pain intensity, HRQoL, sleep quality, physical, and emotional function. These domains have been judged as important in surveys of patients with chronic pain,[25,54] and of health care providers,[24] and are recommended by IMMPACT as core outcome domains.[15,32]

2.2.2. Validated patient-reported outcome measures

Assessment of each domain is based on the following validated PROMs:

(1) Pain intensity assessed with a 100-mm visual analogue scale (VAS) ranging from 0 (no pain) to 100 (worst possible pain).[45]
(2) HRQoL measured with the EuroQol 5-dimension 5-level (EQ-5D-5L) descriptive system that comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and depression/anxiety), where each dimension has 5 response levels: no problems, slight problems, moderate problems, severe problems, and unable to/extreme problems.[28] Responses to the EQ-5D-5L were converted into single (utility) indices using the US value set for EQ-5D-5L crosswalk to EQ-5D-3L.[55]
(3) Sleep quality evaluated with the Pittsburgh Sleep Quality Index (PSQI) instrument that comprises 19 individual items that generate 7 component scores (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime impairment); the sum of the component scores produces a single global score.[6]
(4) Physical function evaluated with the Oswestry Disability Index (ODI) that consists of 10 items/activities each with 6 scoring levels (range 0–5); the sum of the score for each item is divided by the total score possible for the items answered and multiplied by 100.[18]
(5) Emotional function estimated with the Profile of Mood States-Brief (POMS-B) tool that consists of 30 adjectives that describe feelings or moods that an individual may have experienced during the prior week; a total score (total mood disturbance) is derived from 6 mood states (tension, depression, anger, vigor, fatigue, and confusion).[37]

2.2.3. Assessment of unmet health need prior to treatment

Since chronic pain is a personal experience that affects people in different ways, it is important to assess which domains have been impaired on an individual patient basis. This is done by evaluation of baseline (preintervention) status of each patient relative to the normative value for each of the 5 outcome domains. We use published normative values for the 5 outcome domains. Pain intensity: VAS <60 mm (based on inclusion criterion required for study entry in the EVOKE trial of ≥ 60 mm [0–100 mm scale]); physical function: ODI < 10.19[18]; HRQoL: EQ-5D > 0.830[52];

Table 1

EVOKE trial results for 5 individual domains (mean number of MCIDs achieved), cumulative responder score, and holistic minimal clinically important difference score at 1- to 24-month follow up.

Domains	1-mo (n = 111)	3-mo (n = 111)	6-mo (n = 107)	12-mo (n = 103)	18-mo (n = 97)	24-mo (n = 92)
Pain intensity (VAS overall ≥30%)	2.3 (1.0)	2.5 (0.9)	2.4 (0.8)	2.5 (0.9)	2.5 (0.9)	2.3 (1.0)
HRQoL (EQ-5D-5L index score ≥0.074)	3.3 (2.1)	3.5 (2.3)	3.5 (2.1)	3.2 (2.5)	3.3 (2.2)	3.1 (2.2)
Sleep quality (PSQI global score ≥3)*	1.5 (1.4)	1.7 (1.4)	1.6 (1.4)	1.8 (1.5)	1.5 (1.5)	1.5 (1.5)
Physical function (ODI score ≥10)	2.5 (1.6)	2.9 (1.6)	2.7 (1.4)	2.7 (1.5)	2.6 (1.6)	2.5 (1.4)
Emotional function (POMS TMD score ≥10)†	2.3 (1.7)	2.2 (2.0)	2.3 (2.1)	2.2 (2.1)	2.0 (2.1)	2.0 (2.0)
Cumulative responder score‡	11.1 (5.6)	11.9 (6.2)	11.7 (5.9)	11.5 (6.4)	11.1 (5.9)	10.6 (5.6)
Holistic MCID§	2.4 (1.2)	2.6 (1.3)	2.5 (1.2)	2.5 (1.3)	2.4 (1.2)	2.3 (1.2)

Data presented as means and (standard deviations) of MCIDs achieved.
* N of patients with baseline impairment for sleep quality that completed follow-up: 1 month (n = 108), 3 months (n = 108), 6 months (n = 104), 12 months (n = 100), 18 months (n = 94), 24 months (n = 89).
† N of patients with baseline impairment for emotional function that completed follow-up: 1 month (n = 68), 3 months (n = 68), 6 months (n = 67), 12 months (n = 64), 18 months (n = 60), 24 months (n = 58).
‡ Cumulative responder score: the total amount of MCIDs achieved after intervention across all 5 domains impaired at baseline for each individual patient.
§ Holistic MCID: cumulative responder score divided by the number of impaired domains at baseline for each individual patient.
EQ-5D-5L, EuroQol 5-dimension 5-level; HRQoL, health-related quality of life; MCID, minimal clinically important difference; ODI, Oswestry disability index; POMS, profile of mood states; PSQI, Pittsburgh sleep quality index; TMD, total mood disorder; VAS, visual analogue scale.

sleep quality: PSQI <6.3[5]; and emotional function: POMS < 17.7.[37] Domains rated as being worse than normative values reflect areas where patients would place more value on improvements. The holistic MCID score is calculated for those baseline outcome domains demonstrated to score below (worse than) these normative cutoffs.

2.2.4. Intervention response (study outcome) assessed using minimal clinically important differences

Achievement of MCID thresholds are used to assess the intervention response (study outcome) for each of the domains and to calculate the cumulative responder score (sum of the total amount of MCIDs achieved after intervention across all 5 domains impaired at baseline for each individual patient). The following MCIDs were applied: pain intensity: ≥30% decrease in VAS[16]; physical function: ≥10-point decrease in ODI[42]; HRQoL: ≥0.074-point increase in EQ-5D index score[56]; sleep quality: ≥3-point decrease in PSQI[4]; and emotional function: ≥10-point decrease in POMS total mood disorder (TMD).[16]

Table 2

Baseline characteristics and domain scores.

Baseline characteristics	Included patients (n = 111)
Age (y)	56.0 (10.0)
Sex, female (%), male (%)	54 (48.6%), 57 (51.4%)
BMI (kg/m^2)	32.5 (6.2)
Duration of pain (y)	12.7 (10.3)
Race	
American Indian or Alaska Native, n (%)	2 (1.8%)
Black or African American, n (%)	8 (7.2%)
White, n (%)	99 (89.2%)
Other, n (%)	2 (1.8%)
Ethnicity, Hispanic/Latino (%), Non-Hispanic/Latino (%)	6 (5.4%), 105 (94.6%)
Baseline domain scores	
Pain intensity (VAS overall)	82.2 (9.7)
HRQoL (EQ-5D-5L index score)	0.501 (0.137)
Sleep quality (PSQI global score)	13.6 (3.9)
Physical function (ODI score)	55.3 (9.1)
Emotional function (POMS TMD score)	24.8 (18.8)

Data presented as means and (standard deviations) or n (%).
BMI, body mass index; EQ-5D-5L, EuroQol 5-dimension 5-level; HRQoL, health-related quality of life; ODI, Oswestry disability index; POMS, profile of mood states; PSQI, Pittsburgh sleep quality index; TMD, total mood disorder; VAS, visual analogue scale.

2.2.5. Adjustment of holistic minimal clinically important difference score to baseline impairments

To avoid a ceiling effect and to focus on domains where the individual clinical need is greatest, the holistic MCID is calculated by summing each of the MCID domain scores, averaged over each patients' number of impaired domains at baseline (**Fig. 1** for additional explanation on how to calculate the holistic MCID for each individual patient). Worsening in the different domains would have a negative contribution to the cumulative score. The holistic MCID enables standardization of the score irrespective of number of impaired domains at baseline or number of domains considered in a holistic composite outcome (**Fig. 1**). A holistic MCID of 1.0 indicates that a clinically meaningful change was obtained on average across all domains impaired at baseline.

2.3. Data analysis

Internal consistency of holistic MCID was assessed using exploratory dimensional analysis of all domains as a singular "holistic" measure followed by well-established consistency analysis utilizing Cronbach α at each follow-up.[53] Internal consistency dimensional exploration was performed using principal component analysis (PCA), utilizing standard eigenvalue and variance explained analysis visualized with factoextra.[31] Cronbach α statistic and results were computed via the psych package.[48] As a minimum sample size, it is recommended that we would require between 5 and 10 observations for each variable (ie, a sample size of ~50 patients are necessary for the statistical models used in the current study).[12]

To assess the construct validity of the holistic MCID score, 3 approaches were taken. First, comparison of intervention response on the holistic MCID score vs the Patients' Global Impression of Change (PGIC) ordinal 7-category scale (Very Much Worse, Much Worse, Minimally Worse, No Change, Minimally Improved, Much Improved, and Very Much Improved) using ordinal mixed effect longitudinal regression.[10,26] Second, comparison of intervention response on the holistic MCID score vs EuroQol visual analogue scale (EQ-VAS) self-rating scale from 0% (worst imaginable health) to 100% (best imaginable health) using Generalized Linear Mixed Model (GLMM) longitudinal beta-regression.[3,19] Third, use of the take-one-out method removing one dimension of the holistic MCID score and comparing that dimension to the 4-item holistic MCID score using Gaussian Linear Mixed Model (LMM) via lme4.[2] Data cleaning and

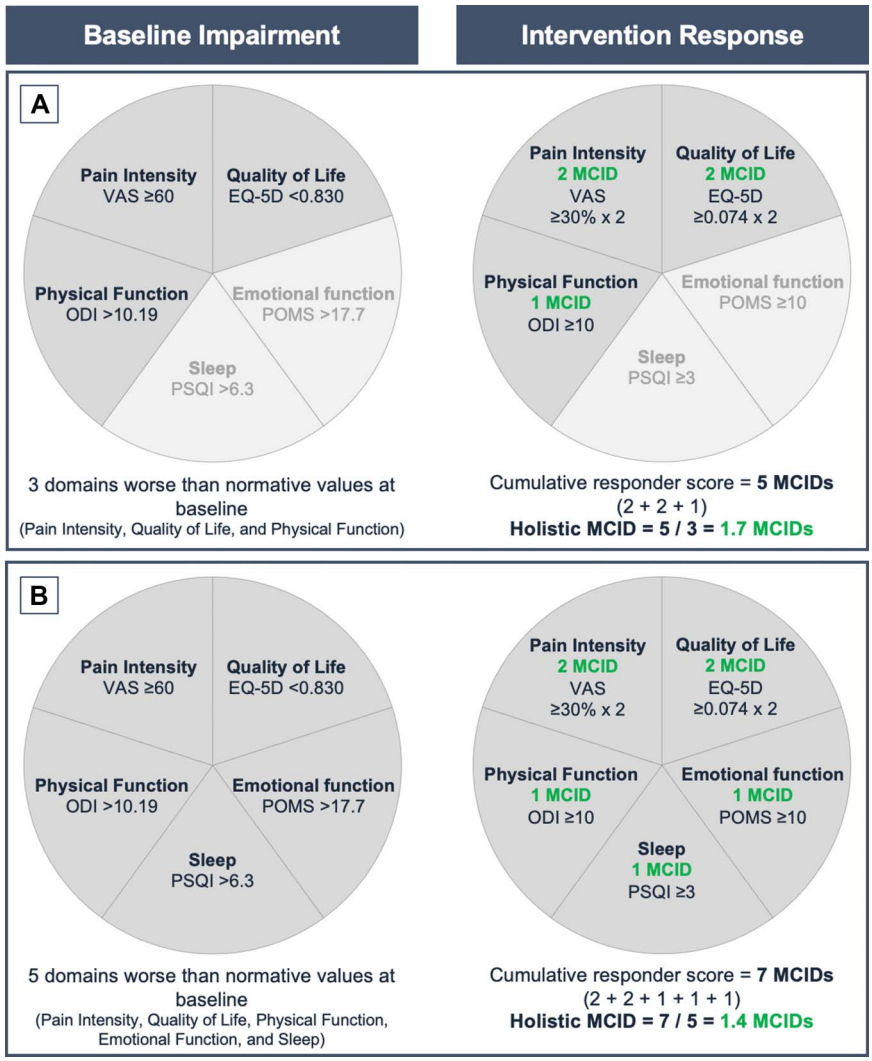

Figure 1. Theoretical representation of the holistic MCID. Five core domains of pain intensity, physical function, health-related quality of life, sleep quality, and emotional function were evaluated. (A) In this example, a hypothetical "Patient A" had baseline impairment for pain intensity, health-related quality of life, and physical function. Patient A obtained 2 MCIDs for each of pain intensity and health-related quality of life domains, and 1 MCID for physical function domain, which corresponds to a cumulative responder score of 5 MCIDs. Adjusting the cumulative responder score of 5 MCIDs by 3 impaired domains at baseline results in a holistic MCID score of 1.7. (B) A hypothetical "Patient B" had baseline impairment in the 5 domains and obtained 2 MCIDs for each of pain intensity and health-related quality of life domains, and 1 MCID for each of sleep quality, physical, and emotional function domains, corresponding to a cumulative responder score of 7 MCIDs. Adjusting the cumulative responder score of 7 MCIDs by 5 impaired domains at baseline results in a holistic MCID score of 1.4.

visualization were performed within the tidyverse.[57] All statistical analysis were performed using R version 4.3.1.[46]

Additional sensitivity analyses were undertaken with the results standardized cross-sectionally by visit to obtain a balanced or equally weighted holistic MCID score (Supplementary material 1, Figs. S1-3 and Tables S1-3, http://links.lww.com/PR9/A256), and each holistic MCID approach was compared to VAS MCID alone (Supplementary material 2, Figs. S4-6 and Tables S4-5, http://links.lww.com/PR9/A256).

3. Results

3.1. Participant characteristics and domain scores before intervention

Detailed characteristics of the patients with chronic pain recruited to the EVOKE trial, number of patients randomized to each treatment group, and results for the randomized controlled trial through 24 months are presented elsewhere.[38,39] A total of 111 patients received a SCS system after a successful trial period, completed the 1-month follow-up assessment, and contributed data to the current analysis. The patients included in the analysis had a mean age of 56 years (SD = 10), relatively equal representation by sex (female n = 54 [48.6%]), and a mean duration of pain of 12.7 years (SD = 10.3) prior to treatment with SCS (**Table 2**).

At baseline, 100% of patients (111/111) presented scores worse than normative population values for pain intensity (VAS), physical function (ODI), and HRQoL (EQ-5D-5L); 97% (108/111) were also impaired for sleep quality (PSQI) and 60% (67/111) for emotional function (POMS). Ninety-eight percent (109/111) of patients presented impaired scores for 4 domains and 60% (67/111) for all 5 outcome domains.

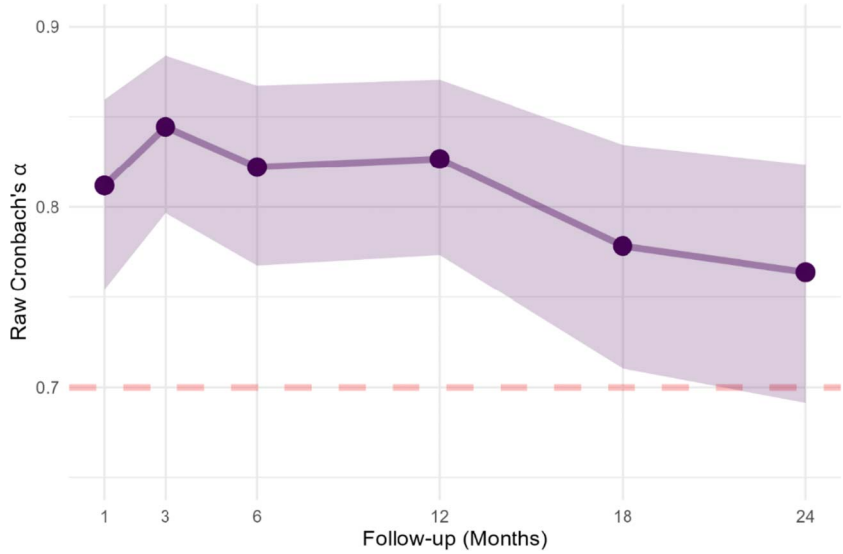

Figure 2. Internal consistency of holistic MCID at each follow-up. MCID, minimal clinically important difference.

3.2. Domain and holistic minimal clinically important difference scores observed in the EVOKE trial

Treatment response assessed using the MCIDs obtained for each of the individual components of the holistic composite outcome, cumulative responder score, and holistic MCID are presented in **Table 1**. Meaningful changes to patients, characterized by ≥ 1 MCID after treatment with SCS, were obtained at all time points for each of the individual domains. The cumulative responder score ranged from a mean of 10.6 MCIDs at 24-month follow-up to mean of 11.9 MCIDs at 3-month follow-up. A holistic MCID of 1.0 indicates that a clinically meaningful change was obtained on average across all domains impaired at baseline. In the current cohort, we observed a holistic MCID >2 at all time points.

3.3. Internal consistency: multivariate dimensional analysis of holistic minimal clinically important difference

A Cronbach α > 0.7 was observed at each follow-up demonstrating strong internal consistency of the holistic MCID outcome (**Fig. 2**). Removing any one of the 5 outcome domains at each follow-up time point did not significantly improve this statistic.

Factor analysis of MCID scores for the 5 individual outcome domains showed one predominant dimension (#1) that included all 5 outcome domains with an eigenvalue of 2.95 (see Supplementary material 3, Table S6, Figs. S7-8, http://links.lww.com/PR9/A256). The eigenvalues of the other 4 identified dimensions were all less than 1 (ie, lower than the average). Dimension #1 explained most of the variance (58.98%). Each of other 4 dimensions explain less than 14% of the variance. There was an equally balanced contribution from the 5 outcome domains to the first component dimension. The analysis supports the holistic 5 outcome basis of the holistic MCID measure.

3.4. Construct validity: holistic minimal clinically important difference association with patients' global impression of change

Due to heavily skewed response rates for PGIC favoring the top 2 categories of improvement "much improved" to "very much improved," and nearly zero observations in the lower categories, responses were collapsed into 3 categories: "minimal improvement, no change, or worse"; "much improved"; and "very much improved." Significant positive associations were observed between increasing holistic MCID score and increased levels of

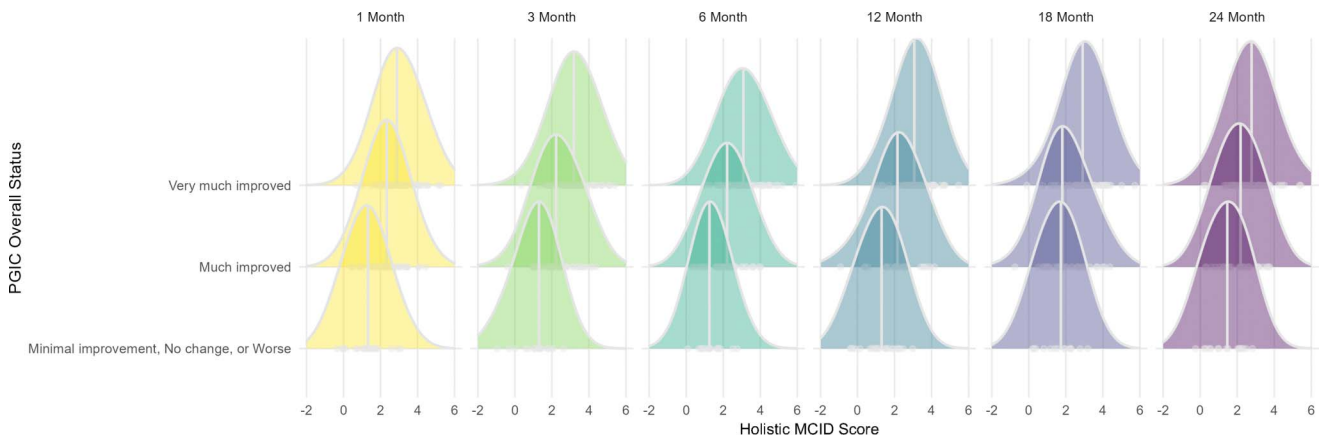

Figure 3. Association between holistic MCID score and PGIC. MCID, minimal clinically important difference; PGIC, patients' global impression of change.

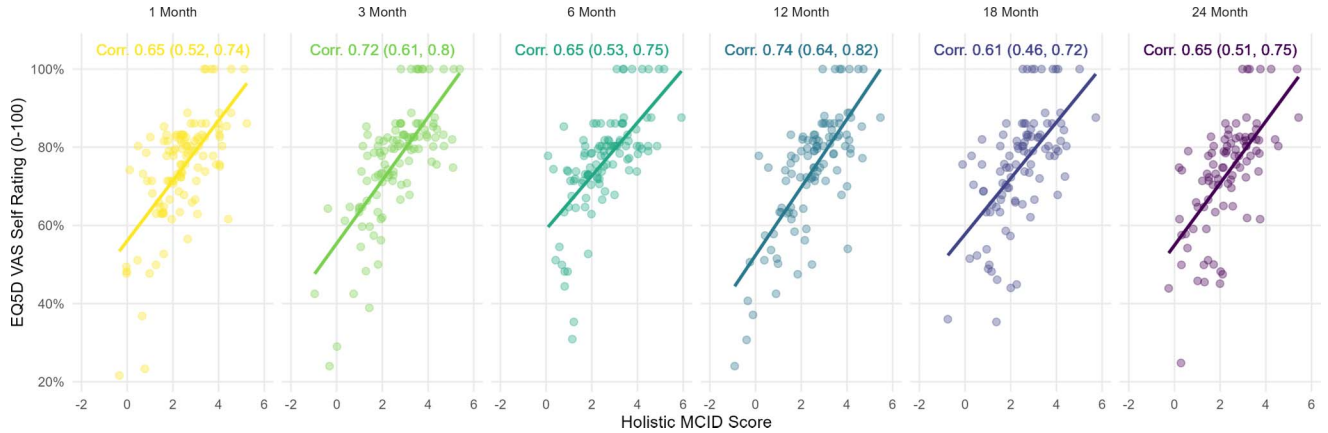

Figure 4. Association between holistic MCID score and EQ-VAS. EQ-VAS, EuroQol visual analogue scale; MCID, minimal clinically important difference.

the ordinal PGIC response at all EVOKE trial follow-ups (**Fig. 3**). While similar positive associations were observed between PGIC response and VAS MCID, the distribution of VAS MCID alone shows uneven variability and less symmetry than the holistic MCID (see Supplementary material 2, Fig. S4, http://links.lww.com/PR9/A256). Therefore, the holistic MCID provides a more balanced or well-calibrated score than VAS MCID alone.

The association between PGIC and holistic MCID is supported by longitudinal ordinal GLMM model, which showed that a one unit increase in the holistic MCID score was associated with an odds ratio of 6.69 (95% CI: 4.62–9.69, $P < 0.001$), ie, relative increase in the expected odds of increasing PGIC category. Full model results can be found in Supplementary material 3, Table S7, http://links.lww.com/PR9/A256.

3.5. Construct validity: holistic minimal clinically important difference association with EQ-VAS

There were strong positive correlations (≥0.61) at all EVOKE follow-up time points between holistic MCID and EQ-VAS (see **Fig. 4**). The holistic MCID scores appeared to be more evenly distributed horizontally, indicating that they are less prone to ceiling and floor effects than seen with VAS MCID scores (Supplementary material 2, Fig. S5, http://links.lww.com/PR9/A256).

Results from the 100% response-inflated GLMM longitudinal beta-regression show for each additional unit increase in the holistic MCID score, an expected 39.1% increase ($P < 0.001$) in the odds of higher EQ-VAS per patient was observed, adjusted for longitudinal correlation and 100% response inflation (Supplementary material 3, Table S8, http://links.lww.com/PR9/A256). Further, this association was approximately 47% stronger than the positive association observed with VAS MCID alone (Supplementary material 2, Table S5, http://links.lww.com/PR9/A256).

3.6. Construct validity: "leave-one-out" 4-item holistic minimal clinically important difference validation

Strong associations (Pearson correlation ≥0.6) were seen across all EVOKE trial follow-ups between the 4-item holistic MCID (minus EQ-5D) vs EQ-5D MCID score (see **Fig. 5**).

These correlations were supported by significant Gaussian LMM results showing a 1.0 unit increase in composite 4-item holistic MCID was associated with an expected 1.44 (95% CI: 1.27–1.62, $P < 0.001$) increase in EQ-5D MCID score (Supplementary material 4, Table S9, http://links.lww.com/PR9/A256). Similarly, significant positive 4-item associations were seen during leave-one-out analyses with omission of ODI, POMS, and PSQI MCID items, respectively, and were likewise observed to be stronger than VAS MCID alone (Supplementary material 4, Figs. S9-S11, http://links.lww.com/PR9/A256).

4. Discussion

The holistic MCID is a composite measure for the personalized and comprehensive assessment of the impact of interventions for

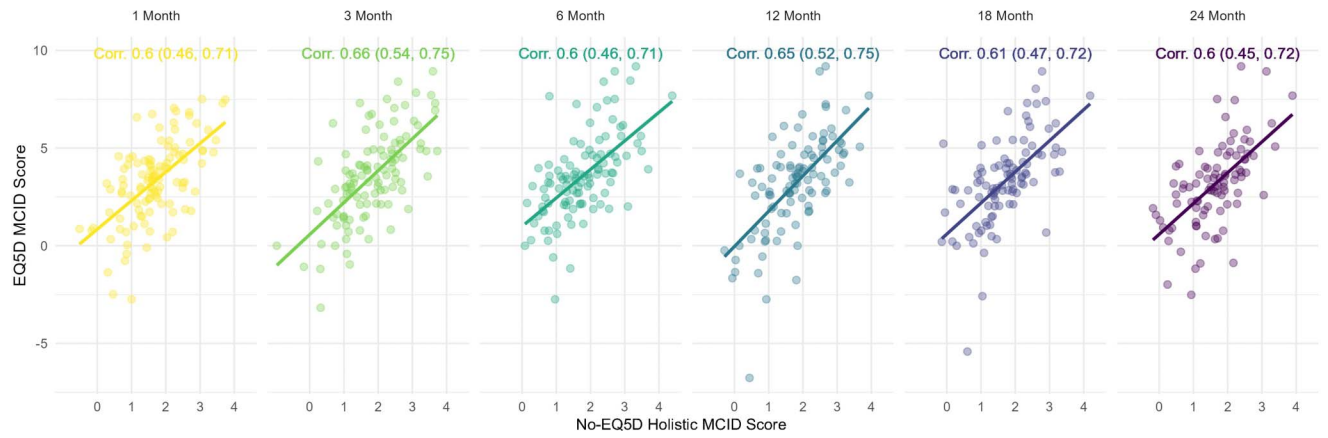

Figure 5. Association between 4-item holistic MCID and EQ-5D MCID. EQ-5D, EuroQol 5-dimension; MCID, minimal clinically important difference.

people with chronic pain. The 5 outcome domains contributing to the holistic MCID were informed by IMMPACT core outcome recommendations and judged as important by patients with chronic pain and health care providers.[15,24,32,54] Formal assessment of the internal and construct validity is a key requirement for the implementation of a new composite outcome in clinical practice, research, and regulatory evaluations. Our study showed consistently high Cronbach alpha (>0.7) at all follow-up time points indicating good internal validity. Factor analysis confirmed that the holistic MCID composite measure is based on an overarching holistic dimension based on all 5 outcome components. Construct validity of the holistic MCID was demonstrated with its strong association with PGIC, EQ-5D VAS, and leave-one-out analysis.

It is now widely accepted that the biopsychosocial model is the most heuristic approach to chronic pain,[21] and that treatment goals and successes encompass more than just pain scores. Yet, there has not been consensus on a methodology that can be used widely and adapted to various chronic pain conditions. Consequentially, different methods have been described for the evaluation of a holistic response,[30,35] such as defining a holistic treatment responder as a patient who obtains a response (≥1 MCID) for each of the domains that were impaired at baseline. This concept of holistic treatment responder is valuable on an individual level and to ascertain the proportion of patients that obtain such a response; however, it does not allow quantification of the magnitude of the holistic treatment effect. Alternatively described is a cumulative responder score, computed as the sum of MCIDs for each domain impaired at baseline. Such a cumulative responder score can, however, be greater or smaller solely on the basis of the number of domains that were impaired at baseline and contribute to the score, or when additional domains are added as components of a holistic composite outcome. Our previous report showed that both the cumulative responder score and holistic MCID can be used to demonstrate benefit of an intervention over an alternative.[30]

Although a number of composite outcomes have been used in chronic pain intervention trials,[1,22,23,44,49] their validity has often not been assessed or reported, and there is a clear lack of consensus. The ACTTION analysis of the validity of 10 different composite outcomes found that 2 composites (≥30% reduction in pain intensity or ≥30% improvement in physical function; ≥50% reduction in pain intensity, or ≥20% reduction in pain intensity and ≥30% improvement in physical function) were more strongly associated with ratings of "much improved" or "very much improved" in the PGIC.[43] The study used a data-driven approach to identify a composite responder score based on level of improvement in pain intensity and physical function (ie, 2 different domains). A limitation of a data-driven approach to development of a composite is that the findings may only be applicable to that specific study population. A recent review observed that composite outcomes of benefits and harms are underutilized in chronic pain trials.[41] Two composite outcomes of benefits and harms were identified, both dichotomous "responder" outcomes that categorized participants into those with or without a favorable outcome.[41] The composite outcomes used a combination of response to pain and absence of stimulation-related neurological deficits[14] or response to pain with no change in baseline pain medications, no discontinuation of the study drug due to lack of efficacy or tolerability, and no moderate or severe adverse drug reactions.[27] It is important to note that these composite outcomes did not consider the breadth of health domains included in the holistic MCID. Nevertheless, separate inclusion of harms in composite outcomes should be further evaluated.

The holistic composite outcome and methods to evaluate treatment response proposed in the current study were informed by previous literature and its framework elaborated by an expert panel.[35] The outcome domains that contribute to the holistic MCID reflect the recommendations of IMMPACT for the collection of PROMs for patients with chronic pain, ie, pain intensity, physical function, HRQoL, emotional function, and sleep quality.[15,32,54] These domains have also been identified as core outcomes for clinical trials in specific pain conditions such as nonspecific low back pain and whiplash associated disorders.[7,9] The selected PROMs have been recommended in core outcome sets for other conditions, including the VAS, ODI, and EQ-5D-5L.[8,51] However, it is important to recognize that other domains or PROMs could contribute to a holistic composite outcome and core outcome sets and PROMs vary widely across different areas of health including chronic pain.[29] A systematic review of PROMs used in chronic neuropathic pain trials found that some 200 different PROMs were used across 251 included studies, and only 27 PROMSs had been recommended by IMMPACT or NeuPSIG guidelines.[50]

The MCIDs used to assess intervention response should be clearly reported and justified. Where appropriate or required, alternative MCID thresholds could be evaluated in sensitivity analysis. The results of the holistic composite outcome should be reported for the composite itself (eg, cumulative responder score or holistic MCID) and for each individual domain to demonstrate the intervention effects on each of the components of the holistic composite outcome. Both the European Medicines Agency[17] and the US Food and Drug Administration (FDA)[20] recommend that the results for each of the individual domains of the composite should also be examined.

To our knowledge, this is the first study to formally assess the validity of a composite outcome to assess the impact of interventions for people with chronic pain. Furthermore, our demonstration of the validity of the holistic MCID was robust to sensitivity analysis.

We recognize that there are some potential limitations to the current study. The data were derived from a single study in a population of patients with significant, treatment refractory chronic pain. It is possible that the results would differ in a population with less severe chronic pain or with different phenotypes of pain. The assumption that participants would place more value on improvements for domains worse than normative values was not directly tested. Our finding of the validity of the holistic MCID outcome should, therefore, be evaluated in other chronic pain populations and interventions. In addition, the treatment response to ECAP-guided SCS showed skewed results in the improvement categories of the PGIC and nearly zero observations in the lower categories, which would reflect a poor treatment response. The wider spread or variability of the holistic MCID score suggests that this metric may be more representative of patients' pain experience when compared with PGIC responses. To overcome the limitations observed with the use of the PGIC, the validity of the holistic MCID was also assessed against the EQ-VAS self-rating scale. The EQ-VAS has been found to have poorer responsiveness but better predictive validity than the EQ-5D-5L index and allows patients to consider more quality-of-life constructs in their subjective rating of health.[36] Comparisons against alternative outcomes, eg, PROMIS-29 or SF-36, would allow further investigation of the construct validity of the holistic MCID.

We observed that the cumulative responder score, without adjustment for the number of impaired domains, is also a valid measure. However, this score may vary considerably solely due to the number of domains that are included in the holistic composite. As such, until there is a consensus on the core outcome domains required to be included in a holistic composite outcome, the holistic MCID score may be more appropriate to compare relative treatment effects. Since the holistic MCID score only incorporates domains for which an individual subject presents worse than normative values, it provides a clinically focused and potentially statistically powerful summary measure. In addition, we also standardized results cross sectionally by visit to obtain a balanced or equally weighted holistic MCID score. Overall, the holistic approach has been shown to be a valuable tool for quantitatively representing a broader spectrum of the pain experience, treatment goals, and treatment successes by combining validated pain intensity, sleep quality, HRQoL, emotional, and physical function measurement, indicating an improved measure to assess the efficacy of interventions for chronic pain. Further studies are warranted on the use of the holistic MCID in other chronic pain conditions where more variability across domains may be present.

5. Conclusion

Pain is subjective and can be difficult to measure objectively—asking a patient to simply rate their pain on a scale of 0 to 10 may fail to consider other factors (eg, function, sleep, emotional well-being, HRQoL) without clarification of the individual's personal meaning of pain.[33] The current study demonstrates that the holistic MCID is a valid composite outcome measure for patients after a chronic pain intervention. By capturing treatment responses across 5 different outcome domains in a single measure, the holistic MCID provides a personalized and more comprehensive measure of the impact of interventions for people with chronic pain than pain response alone.

Disclosures

R.S.T. reports consultancy fees from Medtronic, Nevro and Saluda Medical outside the submitted work. C.M.M. is employed by NAMSA, a company that provides consulting and testing services to medical device manufacturers. N.A.M. reports receiving grants from Neuros, Mesoblast, and Vivex Biologics, as well as consulting as a medical monitor for Saluda Medical, Nevro, Vivex Biologics, Mainstay, Sollis Therapeutics, and Vertos outside the submitted work. J.W.K. is an advisory board member for Boston Scientific, Medtronic, Abbott, and Saluda Medical. J.E.P. reports research and consulting fees from Saluda Medical during the conduct of the study; consultancy for Abbott, Medtronic, Saluda Medical, Flowonix, SpineThera, Vertos, Vertiflex, SPR Therapeutics, Tersera, Aurora, Spark, Ethos, Biotronik, Mainstay, WISE, Boston Scientific, and Thermaquil outside the submitted work; has received grant and research support from: Abbott, Flowonix, Aurora, Painteq, Ethos, Muse, Boston Scientific, SPR Therapeutics, Mainstay, Vertos, AIS, and Thermaquil outside the submitted work; and is a shareholder of Vertos, SPR Therapeutics, Painteq, Aurora, Spark, Celeri Health, Neural Integrative Solutions, Pacific Research Institute, Thermaquil, and Anesthetic Gas Reclamation. C.W.H. has received consultancy fees from Saluda Medical and Genecentrix outside the submitted work. S.J.C. reports receiving grants from Saluda Medical, Vertos, Mainstay, and Vivex outside the submitted work. L.K. reports receiving grants from Nevro, Neuros, Avanos, Medtronic, Neuralace, and Xalud Therapeutics and financial support from Nevro, Avanos, and Saluda Medical outside the submitted work. C.A.G. reports personal fees and other from SPR, and personal fees from Nevro, Nalu, Biotronik, Boston Scientific and Saluda Medical outside the submitted work. E.A.P. has received research support from Mainstay, Medtronic, Neuros Medical, Nevro Corp, ReNeuron, SPR, and Saluda Medical outside the submitted work, as well as personal fees from Abbott Neuromodulation, Biotronik, Medtronic Neuromodulation, Nalu, Neuros Medical, Nevro, Presidio Medical, Saluda Medical, and Vertos outside the submitted work. She holds stock options from SynerFuse and neuro42. K.V.P. is a consultant and speaker for Abbott. S.E. reports consultancy fees from Medtronic, and Mainstay Medical outside the submitted work. He has received department research funding from the National Institute of Health Research, Saluda Medical and Medtronic. R.M.L. is an uncompensated consultant for Biotronik, Abbott, Nalu, Saluda Medical, and Mainstay Medical and has stock options from Nalu and Saluda Medical. C.G. reports payment to his institution (for part of his salary) and stock options received from Mainstay, personal fees from Mainstay, Saluda Medical, Persica, and Iliad outside the submitted work, research funded by Sollis, expert witness testimony fees, and serves as Editor-in-Chief of Pain Practice. S.D. has received consulting payments from Averitas Pharma and Biotronik outside the submitted work. A.A. reports consultancy for Medtronic, Avanos, and StimWave outside the submitted work. P.B. reports consulting fees from Abbott and PainTEQ outside the submitted work. E.H., A.L., N.S. and R.V.D. are employees of Saluda Medical. R.V.D. has previously received consultancy fees from Mainstay Medical, Medtronic, and Saluda Medical. D.J.C. has consulted for AbbVie, Heron Therapeutics, Aptinyx, Neumentum, Regeneron Pharmaceuticals, Swing Therapeutics, Virios Therapeutics, Allergan Sales, Eli Lilly and Company, H. Lundback A/S, Pfizer, Samumed, Tonix Pharmaceuticals. T.J.N. has received consultancy fees from Saluda Medical outside the submitted work. The remaining authors declare no conflict of interest.

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Data availability statement: Saluda Medical is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (eg, protocols and Clinical Study Reports), provided the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research and will be provided after review and approval of a research proposal and statistical analysis plan and execution of a data sharing agreement. Data requests can be submitted at any time, and the data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit https://www.saludamedical.com/us/contact-us/.

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