Responsiveness of Patient-Reported Outcome Measurement Information System (PROMIS) pain domains and disease-specific patient-reported outcome measures in children and adults with sickle cell disease

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Case 1: A 33-year-old man with hemoglobin SS (homozygous hemoglobin S) disease presents for his regular clinic visit. He had 6 hospital admissions for pain over the past year. He also has avascular necrosis of the right hip. He takes daily hydroxyurea with hematologic changes indicative of compliance. He also takes morphine sustained release twice daily and morphine immediate release every 6 hours as needed for pain. He feels that more optimal pain control at home would help him reduce his number of hospital admissions in the upcoming year and improve his daily functioning at home. His hematologist decides to use Patient-Reported Outcome Measurement Information System (PROMIS) and Adult Sickle Cell Quality of Life Measurement Information System (ASCQ-ME) to follow changes in the patient's pain. Case 2: An 11-year-old girl with hemoglobin SS disease presents with her mother for her regular clinic visit. She had 2 admissions for pain over the past year. Her mother is concerned because she has been participating less in activities she previously enjoyed and missing classes to go to the school nurse because of pain. She is currently taking hydroxyurea and uses ibuprofen for pain. Her doctor prescribes morphine for home use but wants a way to measure if it is effective in improving her pain. Thus, her physician decides to use PROMIS and the Pediatric Quality of Life Inventory SCD (PedsQL SCD) module to determine the effectiveness of her pain control.

Learning Objectives

- Review the evidence for responsiveness of pain-related PROMIS domains and disease-specific PROs to acute pain in children and adults with sickle cell disease
- Review the evidence for responsiveness of pain-related PROMIS domains and disease-specific PROs to chronic pain in children and adults with sickle cell disease

Introduction

SCD is the most common inherited blood disorder in the United States, affecting 90 000 to 100 000 individuals and leading to approximately 113 000 annual hospitalizations.[1] The hallmark of SCD is severe pain accounting for the majority of unplanned emergency department visits and hospitalizations. Patients with SCD also suffer from chronic pain, where 29% of adults report daily pain and 40% of children report chronic pain (defined as ≥3 days of pain per week in past month and this frequency for the last 3 months).[2,3] This pain is most often managed at home by the patient and/or family without care in the clinic or hospital.[2] The assessment of pain is complex and ideally incorporates patient self-report.

A robust way to measure pain is to use a PRO tool to determine how pain impacts a patient's function. A multinational study among 58 stakeholders in clinical care and measurement development showed a strong consensus that there is a growing need for more use of tailored PROs in research and clinical practice.[4] To address this need, the NIH developed and made freely available measurement systems for PROs. Among these are HealthMeasures/PROMIS, the SCD-specific ASCQ-Me and the PedsQL SCD module. Before a PRO can be widely integrated into practice, it must be shown to be valid, reliable, and responsive. A pain PRO measure that is multidimensional and able to assess how pain impacts patients' functioning and well-being and that is responsive to changes in pain over time would be a valuable tool for clinicians in the day-to-day management of their patients and for clinical investigators who wish to develop new treatments for pain in SCD.

Through this evidence-based review, we sought to determine the quality of the existing evidence that supports the responsiveness of the PROMIS, ASCQ-ME, and PedsQL SCD Module pain domains to acute and chronic pain over time in both adults and children living with SCD. Anxiety, depression, and fatigue also play important roles in the development and maintenance of pain; however, a comprehensive review of these domains was beyond the scope of this review.

We conducted a systematic review through a search of MEDLINE (1946–present), PubMed, Scopus, CINAHL, and PsycINFO. We

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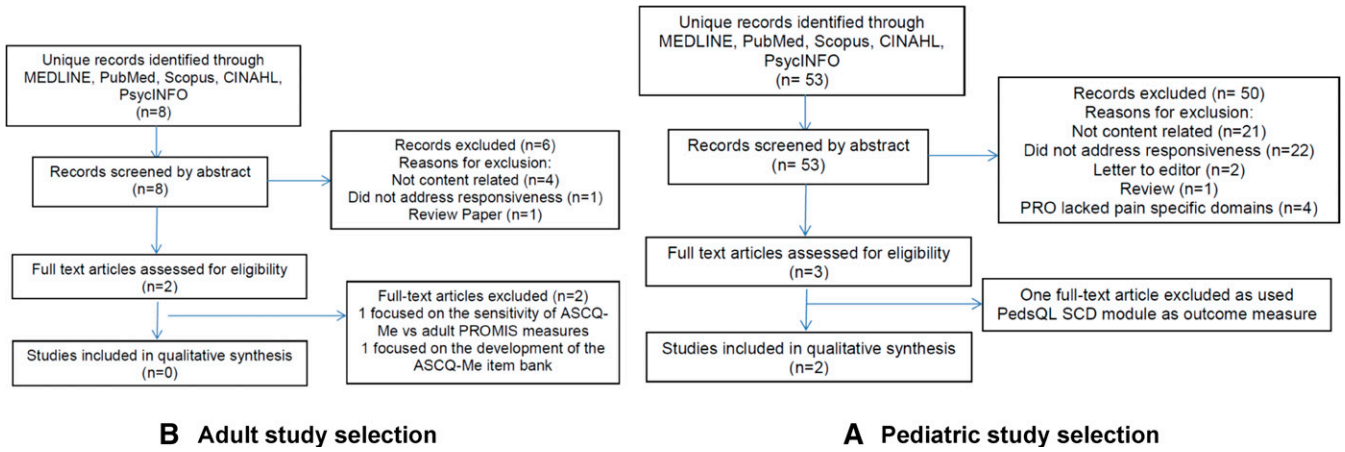

Figure 1. Flow diagrams outlining study selection for evidence-based min-review of the responsiveness of PROMIS pain domains and disease-specific patient-reported outcome measures in children and adults with sickle cell disease. (A) Flow diagram for adult studies that met inclusion criteria. (B) Flow diagram for pediatric studies that met inclusion criteria.

conducted 2 searches, 1 for adults and 1 for pediatrics. Since we were interested in PRO measures that had specific pain domains, general PRO measures were excluded, such as the generic PedsQL. Keywords for the adult search were "sickle cell disease," "PROMIS," "ASCQ-ME," and "pain." Keywords for the pediatric search were "sickle cell disease," "PROMIS," "PedsQL™," and "pain." Figure 1 displays a flow diagram of the article selection process and reasons for exclusion. Results from the final included articles are summarized in Table 1. The GRADE criteria were applied to assess the quality of the evidence.[5] The distinction between GRADE 1a and 1b was made based on the effect size of the change observed with grade 1a designated for studies that revealed large effect sizes (≥0.8) and evidence downgraded for smaller effect sizes (medium effect: 0.5; small effect: 0.2) or if effect sizes were not published but significant changes in mean scores were found.[6]

Adult PRO measures

ASCQ-Me consists of 7 domains: a SCD history checklist and domains that measure pain impact, pain episodes, stiffness impact, sleep impact, emotional functioning impact, and social functioning impact. The domain for pain episodes refers to episodes of acute vaso-occlusive pain events, while the pain impact score evaluates pain over the last 7 days distinguishing acute pain episodes from daily pain.[7] At the time of this review, there were no published studies focused on the longitudinal administration of ASCQ-ME in adults with SCD. Thus, we conclude that there is insufficient evidence to support the responsiveness of ASCQ-Me to detect clinical changes of acute or chronic pain over time in SCD.

PROMIS adult pain-specific measures include pain behavior, interference, intensity, and neuropathic and nociceptive quality. Our literature review revealed PROMIS measures have been evaluated in adults with SCD in a single study by Keller et al.[8] In this study, multiple PROMIS measures including pain impact and pain behavior and all ASCQ-Me measures were administered to 490 adults with SCD. PROMIS measures for pain impact and behavior were worse in patients with more severe disease. Though both PROMIS and ASCQ-Me were able to show variance between SCD severity groups, ASCQ-Me was more sensitive and was able to show variance with fewer items. We found no published longitudinal studies supporting the responsiveness of PROMIS measures to acute pain events or chronic pain in adults with SCD.

In case 1, we would recommend using ASCQ-Me as a one-time measure, as it is valid, reliable, and more sensitive than PROMIS in patients with SCD. However, there is insufficient evidence to support the responsiveness of PROMIS or ASCQ-Me measures to acute or chronic pain over time in adults with SCD.

Pediatric PRO measures

PROMIS pediatric pain domains include pain behavior, pain interference, pain intensity, and pain quality-sensory and pain quality-affective. Pain interference has been shown to be valid in children and adolescents with SCD[9]; however, published data are lacking on the other domains. In a study conducted by Dampier et al., 121 children were administered 8 child self-report PROMIS measures including pain interference during 2 routine clinic visits 1 to 2 years apart and on day of discharge during an admission for an acute pain episode.[10] By comparing the 2 healthy baselines to the values obtained during admission, the PROMIS pediatric pain interference scale was shown to be responsive to changes in acute pain. Specifically, there were significant increases in child self-reported pain interference scores (supporting more severe pain interference) during hospitalization, which then returned to baseline on future follow-up during routine clinic visits[10] (Table 1). We found no other studies using pediatric PROMIS pain measures in patients with SCD in a longitudinal manner. Thus, we conclude that the child self-report PROMIS pain interference scale is responsive to changes in acute pain in children with SCD (grade 1B). There is insufficient evidence to conclude that PROMIS pain measures are responsive to changes in chronic pain over time in children with SCD.

The PedsQL SCD module encompasses 9 scales: pain and hurt, pain impact, pain management and control, worry I, worry II, emotions, treatment, communication I, and communication II. The module has child self-report forms for ages 5 to 7, 8 to 12, and 13 to 18 and parent proxy report forms for ages 2 to 4, 5 to 7, 8 to 12, and 13 to 18 years.[11] In a multicenter study, 243 children and 313 parents completed the PedsQL SCD module measures during a routine clinic visit. The measures were shown to be feasible, reliable, and valid. The pain and hurt and pain impact scores were shown to have the strongest ability to distinguish between children with mild and severe disease.[11] To establish if the measures were responsive to changes in disease status over time, the PedsQL SCD module was administered to 187 patients and caregivers in the emergency department prior to admission for an acute pain event in the context

Table 1. Observational studies evaluating responsiveness of PROMIS pain domains and SCD-specific PRO measures

Author, y	Age, y	Number of subjects	Study setting (inpatient, outpatient)	Type of pain assessed, acute or chronic	PRO pain instrument studied	Study design	Main outcome
Dampier, 2016	8-17	121	At discharge for acute pain exacerbation (inpatient), follow up weeks later after exacerbation (outpatient), clinical visit 1-2 years later (outpatient)	Acute	Pediatric PROMIS Pain Interference domain (child self-report)	Prospective	• PROMIS pain interference domain is responsive to changes in acute vaso-occlusive pain. • Effect sizes were not published; data include significant mean differences with SE between baseline and acute pain.
Panepinto, 2017	4-21	187	At admission for acute pain exacerbation (inpatient), 1 wk later by phone (outpatient), clinical visit 1-3 mo later (outpatient)	Acute	PedsQL SCD Module (Pain and Hurt, Pain Impact, Pain Management and Control; child self-report)	Prospective, ancillary to a clinical trial	• PedsQL SCD Pain and Hurt, Pain Impact and Pain Management and Control domains were responsive to changes in acute pain. • Effect sizes for child self-report as follows: Pain and Hurt (0.91), Pain Impact (0.84), Pain Management and Control (0.45). • Parent proxy-report effect sizes available as supplemental material in paper.

of the magnesium for children in crisis trial (MAGiC Trial).[12,13] The measures were then repeated by phone 1 week after discharge and at a clinic visit 1 to 3 months later. All child self-reported pain measures (Pain and Hurt, Pain Impact, Pain Management and Control) were shown to be similar 1 week and 1 to 3 months post-discharge and worse during the emergency room visits (Table 1). Cumulative distribution scores were also formed for Pain and Hurt, Pain Impact, and Pain Management and Control in order to distinguish what level of change in scores corresponded to clinically meaningful outcomes.[12]

Thus, we conclude that the child self-report PedsQL SCD Pain and Hurt and Pain Impact domains are responsive to changes in acute pain in children with SCD (grade 1A) and the child self-report Pain Management and Control domain is also responsive to changes in acute pain in children with SCD (grade 1B). In our review of the literature, we found no studies that evaluated the responsiveness of the PedsQL SCD module to chronic pain over time in children with SCD. Thus, there is insufficient evidence to conclude that the PedsQL SCD module pain domains (Pain and Hurt, Pain Impact, Pain Management and Control) are responsive to changes in chronic pain over time in children with SCD.

In Case 2, we recommend that either PROMIS or PedsQL SCD be used since no studies have been done comparing the 2 measures.

Acute and chronic pain in SCD remains a clinical outcome vital to the work of both clinical investigators and clinicians. In adults with SCD, ASCQ-Me is a promising PRO tool that is valid and reliable and able to evaluate both acute and chronic pain. However, currently there is no evidence to support its responsiveness to longitudinal changes in acute and chronic pain. Similarly, evidence to support the responsiveness of pain domains from the adult PROMIS measures is also lacking. In the pediatric literature, pain domains from both the pediatric PROMIS measures and PedsQL SCD module have both been shown to be valid, reliable, and responsive to changes in acute pain in children with SCD. Though, to date neither has been shown to be responsive to changes in chronic pain over time. While additional studies of these PRO measures are needed, they represent promising tools for both clinical investigators and clinicians to measure the natural history of SCD pain and the impact of interventions to treat pain in patients with SCD.

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