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Multidomain Patient-Reported Outcomes of Irritable Bowel Syndrome: Exploring Person-Centered Perspectives to Better Understand Symptom Severity Scores

Jeffrey M. Lackner, PsyD[1,*], *James Jaccard, PhD*[2], *Charles Baum, MD*[3]

[1]*Division of Gastroenterology, Department of Medicine, University at Buffalo School of Medicine, SUNY, Buffalo, NY, USA;* [2]*Silver School of Social Work, New York University, New York, NY, USA;* [3]*Takeda Pharmaceuticals International, Deerfield, Illinois, USA*

ABSTRACT

Objectives: Patient-reported outcomes assessing multiple gastrointestinal symptoms are central to characterizing the therapeutic benefit of novel agents for irritable bowel syndrome (IBS). Common approaches that sum or average responses across different illness components must be unidimensional and have small unique variances to avoid aggregation bias and misinterpretation of clinical data. This study sought to evaluate the unidimensionality of the IBS Symptom Severity Scale (IBS-SSS) and to explore person-centered cluster analytic methods for characterizing multivariate-based patient profiles. **Methods:** Ninety-eight Rome-diagnosed patients with IBS completed the IBS-SSS and a single, global item of symptom severity (UCLA Symptom Severity Scale) at pretreatment baseline of a clinical trial funded by the National Institutes of Health. *k*-means cluster analyses were performed on participants' symptom severity scores. **Results:** The IBS-SSS was not unidimensional. Exploratory cluster analyses revealed four common symptom profiles across five items of the IBS-SSS. One cluster of patients (25%) had elevated scores on pain frequency and bowel dissatisfaction, with less elevated but still high scores on life interference and low pain severity ratings. A second cluster (19%) was characterized by intermediate scores on both pain dimensions but more elevated scores on bowel dissatisfaction. A third cluster (18%) had elevated scores across all IBS-SSS subcomponents. The fourth and the most common cluster (37%) had relatively low scores on all dimensions except bowel dissatisfaction and life interference due to IBS symptoms. **Conclusions:** Patient-reported outcome end points and research on IBS more generally relying on multicomponent assessments of symptom severity should take into account the multidimensional structure of symptoms to avoid aggregation bias and to optimize the sensitivity of detecting treatment effects.

Keywords: disease severity, global assessment, health status indicators, outcome research, psychometric properties, questionnaire development, rating scale.

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Introduction

Irritable bowel syndrome (IBS) is a chronic often times disabling gastrointestinal (GI) condition characterized by abdominal pain associated with altered bowel habits (diarrhea, constipation, or both in an alternating manner). With a worldwide prevalence of 10% to 15% [1], IBS imposes a considerable burden on both the individual sufferer and the society as a whole [2,3]. There is currently no satisfactory medical treatment for the full range of symptoms of IBS. Two of the past three drug therapies approved by the Food and Drug Administration (FDA) for the treatment of IBS have required regulatory intervention, leading to drug withdrawal in one case and a severely restrictive risk management program in the other. These events, coupled with recent FDA restrictions on the primary study end point to be used in IBS pharmaceutical development, have reduced the perceived commercial value of new drug development for IBS and limited options for one of the most common GI disorder experienced by patients and seen by physicians in clinical practice [4].

To meet the unmet need for safe and effective treatments for IBS, the U.S. FDA's Study Endpoint and Label Development group has issued a patient-reported outcome (PRO) guidance document [5] that specifies a multistage procedure for evaluating novel agents by using valid and reliable PROs. The FDA regards IBS as one of the top five medical conditions for which a PRO is urgently needed. The process of developing a PRO begins with the delineation of a conceptual framework that clearly describes the relationship among what the PRO instrument is trying to measure (concept), the core signs or symptoms specific to the underlying disease or condition being assessed (domain), and the individual items representative of aspects of the domains; proceeds with both qualitative and quantitative research to define

The views and opinions expressed in this article are those of the authors and not necessarily those of the IBS PRO Working Group of which two of the authors (JML, CB) are members.

* *Address correspondence to:* Jeffrey M. Lackner, Division of Gastroenterology, Department of Medicine, University at Buffalo School of Medicine, SUNY, ECMC, 462 Grider Street, Buffalo, NY 14215, USA.

E-mail: lackner@buffalo.edu.

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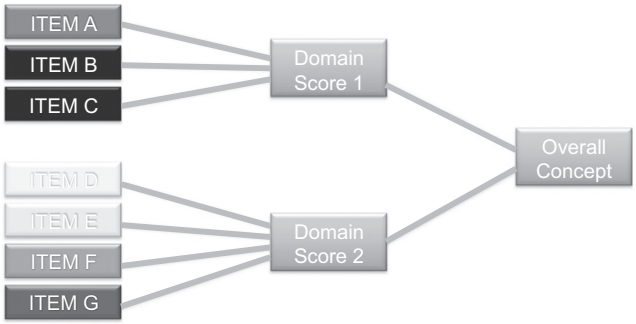

Fig. 1 – Conceptual framework of a patient reported outcome instrument. Adapted from Clin Pharmacol Ther, 84(2), Burke LB, Kennedy DL, Miskala PH, Papadopoulos EJ, Trentacosti AM. The use of patient-reported outcome measures in the evaluation of medical products for regulatory approval, 281-3, 2008, with permission from Nature Publishing Group.

items reflecting those symptoms and establish their psychometric properties; and culminates in the production of a PRO measure that reflects therapeutic benefit from the patient's perspective. Historically, attempts to develop patient-reported end points have gravitated toward the construct of perceived severity of symptoms as a metric for gauging both illness status and the benefit of novel treatments. Representative of this approach is the IBS Symptom Severity Scale (IBS-SSS), a global measure of IBS symptoms that aggregates patient ratings of different, well-defined domains of IBS into a single overall score. The IBS-SSS [6] has been recommended by the Rome Foundation [7] as the global end point for measuring IBS symptom severity in clinical trials. This scale asks individuals to rate four symptom dimensions, each measured on a 0 to 100 rating scale: 1) the severity of abdominal pain, 2) the severity of abdominal distention/tightness (bloating), 3) satisfaction with bowel habits, and 4) life interference due to IBS symptoms. A final item asks the number of days out of previous 10 when the patient experiences abdominal pain, with the answer multiplied by 10 to create a 0 to 100 metric for it.

Like other composite measures developed under the PRO initiative [8], the IBS-SSS generates a total aggregate by summing its items to derive an index of overall symptom severity. Combining items across multiple symptom domains for the purpose of generating a global score is a common practice in PRO development [9]. Theoretically, this approach maps onto the requisite conceptual framework (see Fig. 1) the FDA recommends for constructing a PRO instrument whose overarching measurement focus (concept) is a product of multiple domains (e.g., signs and symptoms). Methodologically, however, aggregating scores from composite items potentiates at least two problems that can make scales misleading. The first problem is aggregation bias. The underlying mechanisms that impact one set of symptoms may differ from the underlying mechanisms that impact another set of symptoms. Aggregating across items obscures such dynamics. One is left with a total score whereby component scores may behave differently in response to a treatment or where the overall score masks a relationship between a component symptom and some other variable of clinical import. For example, a pharmacological treatment may impact defecatory symptoms but have limited, if any, effect on abdominal pain or discomfort. An overall score would then reflect a mixture of change on the item associated with bowel habits and random or systematic "noise" due to the pain items. The result is an index that can mask the true effects of the treatment or make it harder to detect those effects. By the same token, a novel agent may provide some pain relief but little, if any, benefit for defecatory symptoms. An aggregate index will capture both the genuine therapeutic change and the "noise" due to the other components measured by the scale. Aggregation bias represents a serious threat to accurately characterizing patients' experience of their disease and associated treatment, which is the penultimate goal of FDA's PRO guidance document [10].

A second problem is that variation in the total score, all else being equal, is dominated by whichever subcomponent has the most variability across people. If patients exhibit considerable variation on the pain subscale but only modest variation on a subscale about defecatory symptoms such as stool frequency, then variations on the total score will primarily reflect variations in pain, not bowel symptoms. Such a dynamic would advantage agents with strong analgesic properties over those that are primarily designed to relieve defecatory symptoms when using the overall composite score to evaluate a therapeutic agent. This is particularly germane to the IBS-SSS because three of its five items tap abdominal pain or discomfort (pain and bloating severity, number of pain days) and thus likely contribute more variability to the total score. In effect, the IBS-SSS "triple weights" items assessing abdominal pain/discomfort over those assessing nonpain aspects of the IBS experience.

These issues are not necessarily problematic if individual items comprising a multi-item scale are highly correlated and unidimensional in nature. Unidimensional scales measure a single dimension or group of dimensions that cluster with one another. To the extent that a scale is unidimensional and items are highly correlated, the behavior of one item parallels the behavior of other items. The extent to which composite measures of IBS (or for that matter other diseases) are unidimensional is thus an important and largely overlooked psychometric matter critical to the development of sound, meaningful, and sensitive PROs. To our knowledge, IBS end points have been developed without regard to documenting their unidimensional versus multidimensional properties. One purpose of the present study was to examine the unidimensional versus multidimensional structure of the IBS-SSS.

To the extent that individual IBS symptoms are characterized by both nontrivial unique and common variance, it can be useful to identify symptom clusters that characterize significant numbers of patients with IBS. Different treatment regimens might then be implemented depending on the observed symptom patterns, with some therapeutic agents being more appropriate for some types of patients but less appropriate for other types. The present study applied cluster analytic methods to the core symptoms measured by the IBS-SSS with the objective of identifying distinct patient profiles that may require different approaches to symptom resolution. In contrast to traditional approaches that treat each symptom as a separate construct, person-centered cluster analysis uses an idiographic approach that represents the presentation of multiple symptoms as an organized whole [11].

Methods

Participants

Participants included 98 consecutively evaluated patients with IBS recruited primarily through local media coverage and community advertising and referral by local physicians to a tertiary care center at an academic medical center. To qualify, participants must have met Rome II IBS diagnostic criteria [12] without organic GI disease (e.g., IBD and colon cancer) as determined by a board-certified study gastroenterologist. Because this study was conducted as part of a clinical trial for patients more severely affected with IBS, participants must have also reported IBS symptoms of at least moderate intensity (i.e., symptom occurring at least twice weekly for 6 months and causing life interference). Institutional review board approval and written, signed consent

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