Patient-reported Outcomes

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Key points
- Many gastrointestinal diseases are symptom-driven, so the patient’s perspective is particularly important in this area.
- Patient-reported outcomes (PROs) provide essential information that objective measures and clinician assessment may fail to capture.
- PROs can be measured in a scientific, reliable, and valid manner.
- Generic, disease-specific and treatmentspecific PRO instruments exist.
- PRO instruments are valuable for use in clinical trials, to measure treatment outcomes, and also in clinical practice, to describe the burden of illness and to facilitate diagnosis and patient management.

Introduction

The medical community has traditionally preferred to use objective measures to confirm the presence of disease or to monitor treatment response. For example, these could be a positive test for a disease-causing microorganism, such as *Helicobacter pylori*, or the results of an endoscopy showing reflux esophagitis. However, many gastrointestinal (GI) diseases have a high symptom burden but little objective evidence for disease or poor correlation with tests for abnormality. Furthermore, because endoscopic and colonoscopic examinations are not generally performed in primary care, the GI tract is largely inaccessible to further investigation in this setting. Primary care physicians are therefore required to rely on the patient’s subjective report. Symptoms that are only felt by the patient, such as heartburn or abdominal pain, represent the most common self-reported outcome. The classification of medical outcomes into biologic, clinician-reported, caregiver-reported, and patient-reported is shown in Fig. 3.1.

Despite their common use, objective measures do have limitations. The interpretation of objective markers of disease activity, such as endoscopic findings, may differ between clinicians (often referred to as poor inter-rater reliability) [1]. Also, improvements in clinical measures may not correspond to improvements in how a patient feels or is able to function. Some aspects of disease, such as pain intensity and relief, are known only to the patient. In the absence of objective measures, a physician relies on information from the patient in order to make a diagnosis or to assess whether a treatment is successful.

There is therefore a real need to help patients describe their own symptoms in a consistent, standardized way. One way to do this is to use patient-reported outcome (PRO) measures. The US Food and Drug Administration has recently put together draft guidance on the use of PRO measures in clinical
trials to support labeling claims (summarized in Fig. 3.2), reflecting the growing recognition of the value of these tools [2]. In general, patients’ well-being is increasingly being regarded by the medical community as an important factor in assessing treatment response. For example, assessment of PROs and health-related quality of life is now considered to be a standard part of care for patients with gastroesophageal reflux disease (GERD) [3]. The aim of this chapter is to describe some of the PRO instruments available for GI diseases and to review their value both in clinical trials and every-day practice.

What are PRO measures?

A PRO measure is a standardized instrument that assesses any aspect of health status or the benefit of therapy directly from the patient’s perspective. PRO measures include a defined list of items to which patients respond using standardized response options and with respect to a defined recall period. They can be broadly grouped into generic, disease-specific, and treatment-specific instruments (Fig. 3.3).

Generic PROs report overall health and its effect on aspects of everyday life, and can be used in various patient populations. Examples of generic instruments are the Short-Form 36 general health questionnaire (SF-36) [4] and the Psychological General Well-Being index (PGWB) [5]. These measures allow comparisons to be made between diseases but tend to be less sensitive than the more specific instruments to differences within groups of patients with the same condition [6]. In contrast, disease-specific PRO instruments are highly focused on the problems associated with a specific disease and so minimize the amount of “noise” that could be introduced by irrelevant items. These instruments allow patients to describe their symptoms (symptom scales) or the effect that their symptoms have on their lives. Disease-specific measures include the Reflux Disease Questionnaire (RDQ) [7] and the Gastrointestinal Symptom Rating Scale (GSRS) [8]. They also include disease-specific quality of life instruments, which measure how much a particular disease affects activities such as working, sleeping, and eating; examples include the Quality Of Life in Reflux And Dyspepsia (QOLRAD) questionnaire [9] and the Inflammatory Bowel Disease Questionnaire (IBDQ) [10]. Lastly, PROs can be treatment-specific. For example, a PRO could measure specific effects of a certain class of drug or type of therapy, such as the Functional Assessment of Cancer Therapy – Biologic Response Modifier (FACT-BRM) [11].

The value of PROs (Fig. 3.4)

Increasing understanding and recognition of diseases

Many individuals with GI diseases do not visit their physician about their symptoms. For example,
Identify concepts and develop conceptual framework

Create instrument

Assess measurement properties

Modify instrument

• Concepts and domains must be relevant to patients. 
• The intended population and research application should be defined.

• Choose items, recall period, response scales, etc. 
• Patients must be involved in item generation and/or evaluation of content. 
• The content validation process must be documented. 
• Item generation should come from multiple sources. 
• Proof of the importance of content to patients should be sought. 
• Cognitive debriefing should be used to revise measures.

• Reliability: measure test–retest reliability, internal consistency and inter–interviewer reproducibility. 
• Validity: assess content-related validity, ability to measure the concept and predictive validity. 
• Responsiveness: calculate effect size and standard error of the measurement. 
• Interpretability: uncover the clinically relevant difference and responder definition.

• Where necessary, change the concepts measured, populations studied, research application, instrumentation or method of administration.

population-based studies have shown that the majority of individuals with gastroesophageal reflux symptoms do not visit their primary care physician about them [12,13]. This may be because GI symptoms are generally not perceived as serious. Individuals with GI symptoms also often delay visiting their physician until they have another reason to go [14]. Websites, magazines or waiting-room leaflets that include questionnaires about symptoms can alert patients to recognize their true symptom load and its consequences,

Figure 3.2 Summary of the US Food and Drug Administration (FDA) guidance on the development and modification of PRO instruments.

Figure 3.3 Classification of PRO instruments.
thereby encouraging individuals to talk to a physician about GI problems. Leaflets encouraging patients to raise their concerns with a physician have been associated with increased patient satisfaction [15].

PROs can also improve a physician’s understanding of the burden that their patients have. There is increasing evidence of a communication gap between patients and physicians in the reporting of symptoms, which has the potential to lead to underestimation of patients’ symptom burden [16–20]. For GI diseases specifically, data from clinical trials have shown that clinicians tend to underestimate symptom presence and severity and overestimate the benefits of treatment [21,22]. An improved understanding of the effect that GI symptoms can have on quality of life can also help physicians to highlight possible consequences.

PROs in clinical trials

Increasingly, the importance of taking into account the patient’s perspective during drug development is being recognized [23]. In clinical trials, PRO tools can be used to establish the eligibility criteria that should be used, and also the results that can be expected after treatment. PRO tools should be used before other investigations, to uncover baseline levels, and then later, to assess treatment response. Because some treatment effects are known only to the patient, such as relief of pain, PROs can be essential for assessing the effectiveness of treatments in clinical trials.

Tools for diagnosis

PROs facilitate symptom-driven diagnosis. Symptoms are a good starting point for diagnosis because the presence and severity of symptoms drive individuals to consult [12,24]. For many GI diseases, a spectrum of symptoms exists. In the absence of objective evidence, PROs can help to establish a standardized cutoff point at which the severity and frequency of symptoms are considered to indicate disease. For example, heartburn is one of the primary symptoms of GERD, yet over 50% of the general population experience heartburn at least once a year. Clearly not all of these individuals are suffering from GERD. A PRO tool that assesses the frequency and severity of symptoms would assist physicians in diagnosing GERD in a standardized way. PROs that are not yet validated may also contribute to more accurate diagnosis. For example, the Reflux Disease Questionnaire (RDQ) assesses
GERD-related symptoms and gives information on the presence and severity of patient-reported symptoms. This questionnaire has been preliminarily validated for this purpose [25].

Facilitating patient management

PROs can be used after diagnosis, to assist with the long-term management of patients. If physicians are made more aware of the burden of illness that their patients experience, including the effect that symptoms have on patients’ everyday lives, they can more readily assess whether a patient will benefit from treatment. PROs can help a physician to understand the effect that GI symptoms have on health-related quality of life in a standardized way, and so identify where there is a need to treat. For example, the GERD Impact Scale (GIS) is a short, patient-completed questionnaire for patients who have been diagnosed with GERD. It can be used for patients with a new diagnosis, to determine the appropriate level of treatment, and also to help physicians identify currently treated patients who would benefit from changes to their treatment [26].

PROs can help physicians make sure that the most effective treatments are offered to the patients who will benefit most from them. In particular, PROs that evaluate health-related quality of life enable physicians to factor in the patient’s burden of illness when considering how best to manage their symptoms.

PROs may also help to predict response to treatment. For example, a recent study has shown that a high level of anxiety or a low total well-being score at baseline predicts against a positive response to acid suppression therapy [27]. PROs can also predict mortality over and above traditional measures available to physicians, such as history and risk factors [28].

Health economic evaluation

Incorporating PROs into health economic analyses ensures that the benefit of a therapy as felt by the patient is quantified and included in economic decisions. PROs can therefore help make sure that, from a health economic perspective, each individual receives the most appropriate treatment. Standardized ratios such as cost per Quality Adjusted Life Year (QALY) allow the cost-effectiveness of different treatments to be compared. QALYs can also be used to compare treatment outcomes for different diseases, while the derived utility values are useful for comparing the burden of illness of various chronic conditions. PROs can help quantify the savings in cost associated with a treatment. For example, self-rated measurement of increased productivity at work can contribute to assessing the indirect costs saved.

Construction and validation of PRO instruments

The value of a PRO instrument is dependent on the quality of its development, and it is important that patients are involved during this process. Using patient and physician focus groups reduces the risk of measuring irrelevant symptoms. The reliability and validity of each instrument need to be confirmed [29]. In addition, their ability to detect change and interpretability also need to be tested if they are to be used in clinical trials [6].

Limitations of PROs

There are some limitations to the usefulness of PROs. Individuals may not answer honestly, especially if diagnosis of a particular disease via a PRO instrument offers access to treatment. As well as the possibility that they may not remember their experiences and so answer incorrectly, they may seek to fulfill a role as a “good patient.” For example, they may report that their symptoms have improved as they feel that this is an appropriate response after having received treatment or because they feel grateful for the effort that a physician has shown.

Conclusions

Physicians can often underestimate the presence and severity of symptoms, and so there is a clinical need for standardized patient-reported symptom assessment. PROs capture the patient’s perspective directly, and can be measured in a scientific, reliable, and valid manner. PROs are useful both in clinical trials and for symptom-driven diagnosis in clinical practice. They are particularly valuable in diagnosing and assessing GI diseases because many of these diseases have a high symptom burden with little or inaccessible
References

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