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REVIEW

Measuring symptoms and toxicities: a 35-year experience

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Abstract

Purpose When conducting trials aimed at the improvement of cancer-related and/or cancer treatment-related toxicities, it is important to determine the best means of measuring patients' symptoms.

Methods The authors of this current manuscript have an extensive experience with the conduct of symptom-control clinical trials. This experience is utilized to provide insight into the best means of measuring symptoms caused by cancer and/or cancer therapy.

Results Patient-reported outcome data are preferable for measuring bothersome symptoms, for determining toxicities caused by treatment approaches, and offer more accurate and detailed information compared with health care practitioners recording their impressions of patient experiences. Well-validated patient friendly measures are recommended when they are available. When such are not readily available, face-valid, single-item numerical rating scales are effective instruments to document both treatment trial outcomes and cancer treatment side effects/toxicities.

Conclusion The use of numerical rating scales are effective means of measuring symptoms caused by cancer, by cancer treatments, and/or alleviated by symptom control treatment approaches.

Keywords Measuring · Patient-reported outcomes · Clinical trials

Introduction

Accurate assessment of symptoms and toxicities is important for the conduct of symptom control trials. In 1986, our group began a symptom control trial endeavor with early trials developed to evaluate the following problems: cancer-associated anorexia/cachexia, chemotherapy-induced peripheral neuropathy, chemotherapy-associated oral mucositis, and hot flashes in patients with breast and prostate cancers. Since these early stages, our group has been intimately involved with the development of over 150 symptom control trials, most of which have been conducted by means of government-funded, multi-site trials.

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When we initiated this work, some investigators/reviewers advocated for symptoms and toxicities to be recorded by nurses and physicians; patient questionnaire data were considered to be an inferior way to assess these issues. In contrast, we believed, from the beginning of this work, that direct patient-reporting of symptoms and toxicities was more informative than having these items recorded by physicians/nurses. Thus, we have routinely collected patient-reported data over the decades, starting with our earliest studies. Patient reported outcomes (PROs) are now widely recognized as essential for comprehensively understanding and assessing patient outcomes [1–3].

As part of this work, we evaluated a variety of symptoms that had not previously been well evaluated, most of which did not have validated instruments available for measuring patient-reported symptom burden. Instead of dedicating long periods of time to develop validated patient-reported tools, our approach often prioritized face-valid single items, using a practical and intuitive strategy to collect pertinent PRO data for our trials.

We acknowledge that a significant portion of the PRO tools that we used over the last three and a half decades

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were never formally validated prior to us using them. The current manuscript summarizes our experiences to inform PRO tool selection for clinical trials. We will start by discussing the use of PROs in specific topic areas (i.e., cancer anorexia, hot flashes, chemotherapy-induced peripheral neuropathy (CIPN), and mucositis); next, we will provide a more detailed account of how uniscales (e.g., visual analog scales or numerical rating scales) have been helpful for evaluating a wide variety of specific symptoms; lastly, we will elaborate on the use of PROs for the measurement of specific toxicities.

General thoughts

When patients are asked to complete questionnaires at multiple timepoints (monthly, weekly, or even daily for several weeks), it is critical that these questionnaires are simple and brief, to reduce the cumulative time burden and the associated risk of receiving incomplete questionnaires. A questionnaire that can be completed within a few minutes is likely to be completed by many more patients, than are more detailed questionnaires. We have commonly employed intermittent nurse/clinician communications (e.g., phone calls) to encourage patient completion and submission of questionnaires, understanding that patients would still complete their questionnaires independently**.**

Early experience with overall quality of life (QOL) evaluation questionnaires

Decades ago, when we evaluated hydrazine sulfate versus placebo as a potential treatment for patients with advanced colorectal cancer based on its claimed benefit for helping nutrition in patients with cancer (which proved not to provide benefit), we worked with the NCI to evaluate different means of assessing quality of life. While all patients completed a single-item Spitzer uniscale to assess their quality of life, three-fourths of them were also randomly assigned to receive either the 22-item Functional Living Index-Cancer (FLIC) tool, a five-item Spitzer QOL index, or a picture-face scale commonly utilized in young pediatric patients. The results from this trial revealed that there was a strong correlation, concordance, and criterion-related validity among all four studied PRO tools. We concluded, from this work, that the uniscale was an appropriate measure of life quality, in lieu of a more burdensome multi-item questionnaire [4]. Instead of asking patients to rate-specific facets of each QOL construct, a uniscale directly rates a construct as patients personally define it. While longer scales prompt patients to assess a various aspects of health-related QOL and then use a scoring algorithm to calculate overall QOL scores, the uniscale relies on patients themselves to provide an overall quality of life score, acting as their own evaluators. This work led us to adopt uniscales for measuring a variety of specific symptoms and toxicities, as will be discussed in more detail below.

Cancer-associated anorexia/cachexia

Cancer-associated anorexia/cachexia was one of our earliest research topics, with the first treatment trial developed in the late 1980s. Over time, we developed 12 anorexia/cachexia related trials evaluating the following potential therapies: megestrol acetate, dexamethasone, cyproheptadine, hydrazine sulfate, pentoxifylline, fluoxymesterone, dronabinol, eicosapentaenoic acid, etanercept, and olanzapine, the last of which is currently accruing patients [5–15].

The two initial trials, each comparing cyproheptadine or megestrol acetate to placebos, had weight changes as primary endpoints [5, 6]. These trials supported that patient-recorded home weights were as informative as clinic weights. An appetite questionnaire was developed by the investigators for these studies using six single items that appeared to be appropriate to the study purpose and content area (e.g., current appetite compared to before present illness, current food intake compared to before illness, and effect of study medicine on food intake), each with three response options (e.g., worse/same/improved or reduced/same/improved). For each of the items, the Wilcoxon rank sum test was conducted to compare the distributions of the ordered response between two groups. Data from weight changes provided a similar outcome compared to appetite questionnaire changes. A subsequent trial looked at the use of four doses of megestrol acetate, ranging from 160 to 1280 mg/d [7]. Once again, serial weights were determined at physical exams and short questionnaires on appetite, food intake, nausea, vomiting were administered, and the 800 mg/day dose was found to be superior to the lower doses in terms of appetite outcomes, with a tendency for the higher doses to cause weight gain.

By the mid-1990s, we started using weight changes and appetite scores as dual endpoints [12–15]. Presently, we have an ongoing trial, comparing megestrol acetate to olanzapine, with appetite as the primary endpoint, assessed via a single-item eleven-point numerical rating scale (NRS), with weight change as a secondary endpoint. When the sponsoring body and a reviewer raised concerns about the validity of our questionnaires during the review of the last study, we addressed them by highlighting the extensive usage of these questionnaires among over a thousand patients with cancer. Furthermore, in our response to the reviewer, we emphasized the validity of the appetite assessment in the following ways: 1) face validity, evidenced by questionnaire-generated

outcomes reported in high impact journals, such as the Journal of Clinical Oncology and the Journal of the National Cancer Institute; 2) predictive validity, demonstrated by a strong correlation between appetite improvement and weight gain; 3) known-group validity with detection of appetite improvement in treatment arms with orexigenic agents (such as megestrol acetate) in placebo-controlled trials; and 4) concurrent validity with similar results generated when assessed concurrently with the Functional Assessment of Anorexia/Cachexia questionnaire. We had also previously shown good test/retest reliability based on serial, weekly administration of this instrument to patients with cancer. The NCI agreed with us and allowed us to utilize the single item question that we proposed.

One might ask whether it is important to use one specific measure of appetite. A recent meta-analysis reviewed the outcomes of 23 randomized controlled trials of megestrol acetate, involving 3428 patients with cancer [16]. This meta-analysis concluded that megestrol acetate does significantly increase appetite in patients with cancer-associated anorexia, despite the diverse range of outcome measures employed. This supports the notion that there are multiple reliable approaches for accurately measuring the outcome of cancer anorexia/cachexia trials.

Hot flashes

Our first study relating to the treatment of hot flashes was developed in 1989. We created relatively simple daily questionnaires which asked participants to record the number of hot flashes that they experienced each day and how many of them were mild (1), moderate (2), severe (3), or very severe (4). By having patients specifically note the numbers of each of these hot flash categories, per day, we developed a hot flash score (defined as the total number of hot flashes times the mean severity of such hot flashes). Patients were asked to complete this questionnaire daily for five weeks, one week for prospective baseline data and four weeks while on clonidine/placebo. We have consistently had a high degree of questionnaire completion with this approach [17–47]. The estimated time to complete the daily questionnaire is less than one minute. Two separate trials evaluated venlafaxine as a hot flash treatment utilizing this measure, and the venlafaxine curves from these two trials are virtually superimposable [22, 32].

The second time, we proposed to utilize this questionnaire in a clinical trial, a reviewer was concerned because we had not defined, for patients, the characteristics of mild, moderate, severe, and very severe hot flashes. In response to this critique, one of us noted that he had a wife and seven sisters and that he would be afraid to tell any of them, who said they had a severe hot flash, that it was only a mild one! This satisfied the National Cancer Institute reviewers, and we proceeded with the clinical trial. Nonetheless, in response to this reviewer's comment, we asked women who participated in this second clinical trial what they utilized to define a mild, moderate, severe, and very severe hot flash. It was remarkable how uniform these patients' definitions were. This led to a subsequent publication [48] describing this work. These definitions have been provided in subsequent hot flash trials to provide, to the patient, a perspective of how other women defined hot flash severities, while still allowing individual patients to determine the severities of each of their daily hot flashes. Because we also conducted hot flash trials in men with androgen deficiency related to prostate cancer treatment, men were also surveyed regarding how they had defined their hot flash severities; [49] after obtaining this information, such has been provided to men participating in subsequent hot flash trials.

Based on data assessing both the number of hot flashes and the hot flash scores from 9 randomized controlled clinical trials, referenced above, we have learned that outcome results are similar between hot flash frequencies and hot flash scores. Of note, to date, we have used a baseline period of one week, starting from study entry, to evaluate the frequency and severity of hot flashes on a daily basis before initiating the study medication, acknowledging the day-to-day variability of hot flashes experienced by individual patients. Relatively new data, however, support that a single-day baseline assessment of hot flashes is adequate to establish group-level baseline status, because the variations in daily hot flashes for each patient are offset by the numbers of patients in the clinical trial [50].

The methodologies we developed regarding our hot flash trials have been shared with multiple other investigators and were the subject of a previous review manuscript [51].

Chemotherapy-induced neuropathy (CIPN)

Our first CIPN trial, published in 2002 [52], utilized a validated uniscale for measuring pain [53] and a question which had patients select their pain/tingling severity as none, mild, moderate, severe, or very severe [54]. Subsequently, in 2008, we started to utilize the EORTC CIPN 20 instrument in a trial evaluating a topical preparation of baclofen, amitriptyline and ketamine; we have used it since, in several additional trials [55–63]. This instrument has been well-validated [64, 65]. Endpoints for conducted trials can utilize data from 1) all 19 or 20 questions (noting that one question is only applicable to males as it deals with erection symptoms), 2) nine questions which have been labeled as a sensory subscale, or 3) six questions which deal with numbness, tingling, and pain in upper and lower extremities. Once

a patient is familiar with this questionnaire, it can typically be completed within a couple minutes.

We also developed and used daily questionnaires to better understand the aspects of acute neuropathy problems from paclitaxel and oxaliplatin [56, 59]. To our knowledge, they are the only available PRO instruments for these problems.

Mucositis

Our first mucositis study was developed in 1986. At that time, mucositis, in treatment clinical trials with drugs such as 5-FU, was commonly assessed by asking the physicians/nurses to query the patient about the mucositis symptoms that they had experienced during the weeks since they had received 5-FU, and record such in the clinical record. We hypothesized that it would be more accurate to ask patients to record mucositis severity daily, for 30 days, after receiving 5-FU, to avoid retrospective bias in clinician ratings conducted weeks later. Thus, we developed a questionnaire to have patients record mucositis severity. While many of our proposed and studied antidotes did not decrease mucositis, we were the first, using data from a protocol developed in 1989, to demonstrate that oral cryotherapy substantially decreased FU-induced mucositis, something that has been replicated multiple times, by other investigators, and is now recommended by mucositis guidelines [52, 66, 67]. This replication of results by other investigators serves as validation of our measurement methods, which included visual analogue scale (VAS) or verbal descriptor scale with five answer choices to measure their symptom.

While we could provide further examples of "common sense" PRO symptom measurement development for other symptoms that we have studied, we will not do so, given that the outcomes are similar to the four examples provided above.

Visual analog scales (VAS) and numerical rating scales (NRS) for the measurement of symptoms and toxicities

A VAS is a response format on a line between two endpoints to record numerical ratings on a continuum. Respondents specify, on the continuum, their experience of symptoms or level of agreement to a statement, by indicating a position on the line. The two endpoints represent the most extreme values. A classic VAS, if completed on paper, requires a scorer to use a ruler to obtain the score and is therefore cumbersome. It also poses risk of inaccuracy, as stray marks from the patient can make it challenging for the scorer to know exactly which marks are intended to convey symptom severity. The EQ VAS, developed by the EuroQol Group, is an example of a thermometer-style VAS, which includes markings that eliminate the need for manual scoring with a ruler. The two endpoints on the EQ VAS indicate the worst health/symptom you can imagine and the best health/symptom you can imagine. The continuous aspect of the VAS scale differentiates it from more discrete scales such as the Likert scale or NRS.

Many studies have demonstrated psychometric soundness of VAS or NRS measures [68, 69]. Specifically, the VAS for cancer pain intensity has been shown to have sensitivity to changes in cancer pain associated with treatment or time, strong associations with other pain intensity ratings, performance status, measures of psychological distress, and measures of global QOL.

An NRS is commonly administered on an 11-point scale from 0 to 10. The most extensively validated NRS response scale has two extreme categories labeled (e.g., no pain at all, worst imaginable pain) with only integers and no descriptors in between. Patients are asked to write down, circle, or say the single number that best represents their status on this scale. NRS items may be called visual NRS (VNRS or VRS) when the scale is shown on paper to the patient. NRSs have been shown to have very strong associations with VASs. The reliability and validity of NRSs have been studied extensively [68, 70]. The brief pain inventory (BPI) developed in 1994 [71] includes NRS items that ask pain at its worst, pain at its least, and pain on the average in the last week, and pain right now. The Edmonton Symptom Assessment System (ESAS), developed in 1991, is one of the first quantitative symptom assessment batteries for symptom management, has been translated into over 20 languages and is composed of VAS items (later adapted to NRS items) on pain, tiredness, drowsiness, nausea, lack of appetite, dyspnea, depression, anxiety, and wellbeing [72]. It has shown good test–retest reliability, has concurrent validity evidence with the BPI and Rotterdam Symptom Checklist, has correlated with Functional Assessment of Cancer Therapy [FACT] pain or Memorial Symptom Assessment Scale in an expected direction, predicted emergency room visits and survival, and has been shown to have good discrimination for symptom change [73]. Because it is easy to understand, complete, and score, NRS works well with low literacy levels and is preferred by patients in different cultures [74, 75].

Studies have illustrated the contexts in which single items may be appropriate. For example, in cancer clinical trials with the overall emotional functioning as an exploratory endpoint, a comprehensive approach may not be appropriate or feasible [76], and single-item measures that target the overall emotional functioning may suffice. Although less specific or precise, if the goal of the measurement is only the global impression of a construct, single items may be valid for the intended purpose. In addition, a single item may be suitable for specific and unambiguous symptoms [77]. As

the complexity of a construct increases, more items may be needed. On a related note, the FDA guidance document states that the conceptual framework of a PRO instrument may be straightforward if a single item (e.g., pain intensity) is a reliable and valid measure of the concept of interest [78].

The NRS items have become the most-used assessment in all NCI-sponsored cancer control studies. Psychometric evaluation of NRS in patients with cancer [79] support that NRS items show adequate variability to be clinically meaningful, avoiding restriction of range and discriminating across individual patients and across time. NRS also strongly correlate with well-validated scales measuring similar domains. In a study that compared the responsiveness between mood NRS and a multi-item mood scale (Befindlichkeits-Skala (BF-S) or ZERSSEN Mood Scale) that produces a mood/emotional well-being score in two International Breast Cancer Study Group (IBCSG) randomized clinical trials [76], it was found that the BF-S was more efficient overall at detecting changes in emotional well-being from adjuvant treatment compared to single-item mood NRS. However, the mood NRS was more responsive to recurrence, and in certain situations, the direction of change for only the mood NRS was in agreement with clinical judgment.

In light of the data presented above, we have used VAS/NRS for measuring more than 25 symptoms within our symptom control program, including symptoms targeted by our proposed treatments that we are trying to improve and symptoms that represent potential toxicities of our treatment approaches.

Toxicity assessment

While much of the above discussion deals with measurement of symptoms that may be amenable to treatment, any of these symptom-focused treatments may have side effects of their own. Thus, it is important to measure the toxicities of the investigational treatments. Many of these toxicities do not have validated measures to evaluate them. In recent years, the utilization of PROs has become a common practice to evaluate toxicities, and we feel that this is much preferred over clinician assessment as we believe that the assessment of symptoms that we are trying to treat, such as mucositis, neuropathy, and hot flashes, are best done by the direct report by the patient who experiences them.

When we assess symptoms that we are trying to mitigate and potential treatment-related toxicities, we commonly employ numerical analog scales (NAS) before initiating the treatment approach under investigation and at various intervals thereafter, without telling patients whether each item pertains to 1) expected improvements from the treatment versus 2) potential treatment-related toxicities. This approach is designed to minimize response bias as patients report their experiences without being influenced by predefined expectations or concerns.

This approach has led to surprising findings at times. In our first trial evaluating megestrol acetate as a treatment for cancer-associated anorexia/cachexia, we included nausea and vomiting questions four weeks after study initiation. Initially intended as a side effect assessment, we aimed to determine whether megestrol acetate would lead to nausea and/or vomiting. What we discovered, however, was that patients on the megestrol acetate arm had about one-third as much nausea/vomiting as did the placebo group, suggesting that megestrol acetate might also have unexpected antiemetic properties [6]. The nausea and vomiting incidences in the placebo-control arm of this trial were not trivial, affecting 38% and 25% of patients, respectively. In this trial, we did not ask about nausea or vomiting at baseline, which taught us to routinely ask for potential toxicities at baseline. In a subsequent trial, we compared megestrol acetate to placebo in newly diagnosed patients with small-cell lung cancer asking nausea/vomiting questions at baseline and follow-up; this work confirmed that megestrol acetate has antiemetic properties [11].

Concluding remarks

As opposed to clinician reports, PROs directly assess the patient experience and thus are preferable for symptom and toxicity assessment. Investigators must carefully consider the purpose of their study before selecting the appropriate measurement tools. In the absence of well validated patient-friendly measures, face-valid, single-item NRSs have proven to be effective instruments for documenting treatment trial outcomes and cancer treatment side effects/toxicities. Single-item NRSs can also help reduce patient response burden when multiple measurements are taken over time. When justified by the context, the use of NRSs can be a highly effective approach for measuring symptoms caused by cancer, by cancer treatments, and/or alleviated by symptom control treatment approaches. This approach substantiates the development and use of the NCI's PRO-CTCAE instruments [80, 81].

Author contribution Charles Loprinzi wrote the first draft of this manuscript, coordinated edits, and completed the last draft. All of the other authors provided substantial input into many drafts of this manuscript and approved the final version of such.

Data availability This is not applicable for this review manuscript.

Declarations

Ethical approval There was no ethical committee review as this is a commentary-type manuscript, as opposed to a clinical trial. Mayo ethical committee does not require approval for the current manuscript.

Consent to participate This is not applicable for this review manuscript.

Competing interests Dr. Loprinzi reports personal fees from PledPharma, personal fees from Disarm Therapeutics; personal fees from Asahi Kasei/Veloxis; personal fees from Metys Pharmaceuticals; personal fees from OnQuality; personal fees from Mitsubishi Tanabe; personal fees from NKMax, personal fees from Novartis; personal fees from HengRui; personal fees from Nuro Bio, personal fees from Osmol Therapeutics, Inc.; personal fees from Grunenthal; personal fees from Genentech outside the submitted work; personal fees from Bexion outside the submitted work; personal fees from Emmes Company outside the submitted work; personal fees from Pfizer outside the submitted work; and personal fees from Toray outside the submitted work. He also reports royalties from UpToDate. Dr. Ruddy reports royalties from UpToDate.

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