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Assessing Psychological Toxicity and Patient-Reported Distress as the Sixth Vital Sign in Cancer Care and Clinical Trials

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Abstract

As the number of available cancer therapies continues to grow, there is increasing interest in their impact on cancer patients' lived experiences. Screening for distress is one way to measure psychological dimensions of cancer patients' experiences, and doing so is increasingly part of standard operations at major cancer centers across the US. To date, however, most clinical trials have not adequately captured patients' experiences as part of their outcome assessments, so clinicians lack data needed to guide their responses to psychological features of patients' illness experiences. As distress becomes the "sixth vital sign" in routine cancer care, we argue that clinical trials should assess patients' experiences in the same way that they robustly screen for adverse events and toxicities. New interventions are needed to address distress.

Introduction

After many years of exclusive emphasis on physical symptoms and clinical outcomes, the twenty-first century has ushered in heightened attention to psychological issues in cancer care. In 1999, the Institute of Medicine (IOM) (now the National Academy of Medicine) published a report, *Ensuring Quality Cancer Care*, which outlined psychological distress assessment and management as a core component of quality cancer care [1]. Then in its landmark 2008 report, *Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs*, the IOM more strongly recommended that psychological assessments be integrated into routine cancer care [2]. Shortly thereafter, the International Psycho-Oncology Society (IPOS) recommended a revision to cancer care standards and clinical practice guidelines, ranking distress as the "6th vital sign" in cancer care [3, 4]. These recommendations have since been translated into cancer center accreditation requirements [5].

While these recommendations are quite clear, their justification and evidence base until recently have been a bit murkier. Ensuing discussions have raised important questions about the concept of "distress," the reliability of measurements thereof, and the implications of these recommendations for clinical practice and research [6-9]. We argue that the evidence supporting the guidelines is now clear and that there is ultimately an

ethical imperative to follow the IOM and IPOS recommendations in routine clinical care. Taken to its logical conclusion, this argument also suggests that we should incorporate assessments of distress into oncology clinical trials as well. We will discuss and defend this viewpoint here.

Distress is Measurable and Actionable

While the notion of distress may sound vague or confusing to some, it actually has a rather specific definition. The National Comprehensive Cancer Network® (NCCN®) defines distress as "an unpleasant emotional experience associated with the psychosocial complications of cancer that may interfere with quality of life" [10]. As such, distress encompasses more than just anxiety or depression, although it does include these experiences within its broader scope. For example, evidence demonstrates the close relationships between physical symptoms, like pain and constipation, and emotional distress [11]. In other words, various experiences can cause distress among patients with cancer: physical symptoms can be distressing, but so are financial hardships as well as emotional challenges like anxiety or depression.

Distress has also been the topic of a great deal of research in oncology in the last decade. For example, evidence suggests that distress is quite prevalent among patients with cancer; one study estimates its prevalence is as high as 35 percent [12]. Yet it is frequently overlooked or inadequately addressed in practice [13]. Patients who are facing a serious illness like cancer deserve to have their distress assessed and addressed, and we are not alone in this view; our perspective aligns with recommendations from the most recent IOM report in this area, *Delivering High-Quality Cancer Care: Charting a New Course for a System in Crisis* [14], which emphasizes the need to collect more data directly from patients to better understand their needs and experiences [15]. As such, we argue that personalized cancer care must include the systematic assessment of, and attention to, patients' experiences, including but not limited to distress.

As a defined construct, distress is readily measurable. Several standardized, short scales are available to measure distress, including the NCCN's "Distress Thermometer" (DT), one of the most widely-used validated scales with people affected by cancer [16, 17]. The DT is a simple 0 to 10 ordinal scale that looks like a thermometer; it allows patients to quickly rate their overall level of distress. In addition, its accompanying "problem list" includes a set of 39 items in 5 domains of well-being, allowing patients to quickly mark "yes" or "no" to any issues that may be contributing to their distress in physical, family, practical, emotional, and spiritual/religious domains [18].

In 2015, the American College of Surgeons Commission on Cancer® (CoC) instituted an accreditation requirement for comprehensive cancer centers regarding distress screening [5]. Meeting this guideline requires a program to integrate psychosocial

experts into the cancer center to vet and select a distress screening instrument, determine timing and frequency of screening, develop a referral management plan, and document the entire process. Given the number of cancer centers accredited through the CoC [19], it is likely that this new mandate has significantly increased the use of distress screening in clinical practice. What has not followed as quickly, however, is the development of more systematic, rigorously tested and implemented interventions to actually address this distress in routine clinical care and in clinical trials.

Amid this gap, we often hear our colleagues complain that distress scores are not particularly actionable in daily practice. In other words, many clinicians are unsure of how to interpret the results of distress screening or what to do about abnormal results. They might expect that distress is occurring due to side effects of treatment and perhaps believe these side effects cannot be mitigated and will improve on their own with time. Or they might feel ill equipped to "fix" problems related to anxiety or depressed mood. Similar critiques have been levied against systematic quality of life assessments in routine practice [20].

To the contrary, emerging data now suggest there are distinct benefits conferred by regular distress screening and symptom or quality of life assessment among patients with cancer. For example, in a study comparing patients who received care either before (n = 740) or after (n = 534) implementation of routine distress screening and appropriate interventions, patients in the post-implementation cohort showed significant improvements in psychological and physical symptoms as well as psychosocial well-being [21]. Follow-up analyses in this study assessed clinician confidence in managing distress and demonstrated significant improvements therein [22]. Similarly, in a large randomized controlled trial conducted by Basch et al., investigators found that patients who participated in weekly symptom monitoring via tablet computers actually had improved overall quality of life over time [23]. Furthermore, recent work by our group in specialty palliative care demonstrates that more comprehensive and frequent assessments of distress are associated with higher quality of life among cancer patients living in the community [24].

We contend that these findings, among others, substantiate the decision by IPOS to recommend distress assessment as the sixth vital sign and provide compelling data to reinforce the National Academy of Medicine's recommendation from over a decade ago. Not only are these kinds of "softer" patient-reported data readily collectable in a reliable manner, but they are also amenable to intervention. Most importantly, the systematic inclusion of distress screening and management into routine cancer care practices appears to improve patient-centered outcomes, as discussed above.

Clinical Trials' Emphasis on Physical Toxicities over Psychological Ones

While distress screening is increasingly common since the CoC issued its accreditation mandate, distress data remain relatively scarce in oncology clinical trials. Standard outcome assessments in drug trials include expected measures of disease response to treatment, such as response rate or progression-free survival. They also include standard toxicity assessments such as the Common Terminology Criteria for Adverse Events (CTCAE), a standardized clinical trials toxicity-reporting instrument for assessing adverse events that allows comparison across trials and may include other patient-reported outcome measures of overall quality of life. Measures of distress, or "psychological toxicity" as one might call it, have not generally been collected as part of drug trials, despite the fact that distress is indeed a predictable "toxicity" of cancer treatment and that distress screening tools have existed for at least 20 years. As such, we have a very limited understanding of the degree of distress seen in different diseases or across different treatment regimens, even within randomized controlled trials, which provide the most rigorous level of evidence in medicine. The same is true for quality of life, which is not measured in many oncology drug trials or often not reported in landmark publications of initial results [25].

We therefore argue that, beyond its inclusion in standard care assessments as the sixth vital sign, more systematic, regular assessment of psychological well-being should be part of clinical trials and other research efforts in oncology, in part to help remedy this knowledge gap. Such assessments can be implemented easily alongside other patient-reported outcome assessments of demographics and medical history (e.g., routine intake forms prior to appointments) or toxicity and efficacy assessments (e.g., symptoms) during routine clinical care that also serves to support research [26]. Calls have been made for drug trials to assess adverse symptom events, including distress as a toxicity measure [27] (i.e., psychological toxicity), and we suggest that novel interventions to address distress must be developed and rigorously tested, just as clinical trials test novel cancer therapeutics.

Ethical Considerations and Future Directions

In light of the growing data about psychological toxicity and distress as presented above, we therefore argue that there is an ethical imperative to measure and address distress as part of clinical care and research endeavors, including clinical trials. Survival and progression-free survival, two of the most common clinical trial endpoints, are not the only important endpoints for patients. Indeed, for patients and patient advocates, the patient experience itself matters, and it matters a lot [28]. It can matter even more than the estimated increases in overall survival seen with many approved novel oncology drugs, which are sometimes only in the order of 12 weeks or less [29, 30]. We envision a future in which patients will report their symptoms, quality of life, and distress on electronic devices as part of routine care, and that these data will serve as actionable items in their care, helping us to better understand and meet the needs of those who are

facing serious illness. This will enable us to further test, refine, and disseminate interventions that improve patients' experiences. Such is truly "personalized medicine," in its most personal sense, as it addresses those things that matter most to an individual, in an effort to improve his or her life. Patients and families deserve the best care we can provide, and that includes assessing and addressing distress as a core component of comprehensive cancer care and clinical trials.

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