Cancer patients experience multiple distressing symptoms. Pain has long been recognized as a common burden for patients with cancer. As described in prior issues of *Pain: Clinical Updates*, tremendous efforts have focused on understanding mechanisms of cancer pain and developing new drug, nondrug, and interventional approaches for its management. The recent upgrading of the priority of cancer pain management is reflected in numerous clinical practice guidelines and quality improvement standards. Yet pain is but one of a complex of symptoms experienced by cancer patients, and it has become clear to oncology caregivers and researchers that patients with advanced cancer, those who undergo aggressive cancer treatment, longer-term survivors, and even those in remission are affected by other symptoms including fatigue, depression, and sleep disturbance.

Pain is but one of a complex of symptoms experienced by cancer patients.

Just as pain itself received inadequate attention from cancer clinicians in the past, these other non-pain symptoms are often underassessed and undertreated. Persistent non-pain symptoms not only cause distress and impede function, but may indirectly affect patient survival by compromising adherence to treatment, or even causing premature termination of treatment. The collective effect of these symptoms, or “symptom burden,” is the subjective counterpart of tumor burden. Reducing symptom burden will require a deeper understanding of the nature of symptom development and an improvement in strategies for symptom management, both of which are the mission of symptom research. This issue of *Pain: Clinical Updates* focuses on this still-young field with its many promising research opportunities.

Non-Pain Cancer Symptoms and Clusters Are Important

The need for new approaches to the management of multiple, clustered symptoms in cancer is well recognized. The Institute of Medicine of the U.S. National Academy of Sciences lists the control of cancer-related pain, depression, and fatigue as one of the top 20 priorities for improving health care. Just as for estimates of pain, published estimates of the prevalence of major depression in patients with cancer vary widely. Assessments performed in patients with different types and stages of cancer and in outpatient versus inpatient settings indicate that from fewer than 1 in 10 to nearly half of patients meet DSM criteria for major depressive disorder and clinically significant depressive symptoms. The most
common published estimates across all settings are about one in every five to six patients. Even wider estimates of fatigue (4–91%) have been described in patients with cancer studied during treatments such as chemotheraphy and radiation therapy. Roughly half of patients receiving palliative care and almost half of cancer survivors report fatigue, although the instruments used to assess its presence have not been standard. Most studies of fatigue have used multi-item, multidimensional assessment methods.

Faced with the substantial prevalence of non-pain symptoms, and noting that the feasibility of symptom-control studies has been demonstrated, the National Cancer Advisory Board of the Institute of Medicine has called for a significant increase in symptom-directed research. Recent trends cited in that report, which indicate that symptom control is likely to become even more important, include the growing acceptance of subjective patient reports about symptoms as reasonable measures in clinical and experimental research; the acceptance of quality-of-life outcomes—including aspects of symptom control—as clinical trial endpoints; the development of new technologies that offer insights into the nature, mechanisms, and expression of symptoms (e.g., brain imaging techniques to study pain and depression, bioinformatics to deal with large databases of biological and subjective data, and genotyping to identify individuals at high risk of developing symptoms); and advances in neurobiology and molecular biology that shed new light on how symptoms arise and the variability in their expression among individuals.

Mirroring observations from the clinical literature on noncancer pain, in which symptoms such as anxiety or depression cluster around pain, pain and non-pain cancer symptoms often present simultaneously and may exacerbate one another. Many clinicians have observed the phenomenon that certain severe symptoms appear in combination across various forms of neoplasia and cancer treatments. For example, pain is often linked with distress, sleep problems, difficulties with concentration, and fatigue. Post-treatment symptoms (e.g., fatigue, cognitive deficits, neuropathy) can co-occur to limit vocational activity and inhibit social reintegration. Treatment-related symptoms can even affect survival if they become so severe that patients abandon potentially curative therapies. Relieving symptom burden, whether caused by the disease or by treatment, not only is essential for improving quality of life in patients with cancer, but also has potential benefit for survival.

Treatment-Related Symptom Burden

Reducing the burden of treatment-related symptoms upon a patient’s functional status throughout the trajectory of cancer, especially during and after aggressive curative therapy, should be an important goal of cancer care. However, optimal symptom control depends on understanding the mechanisms by which physical and psychological symptoms develop over the course of treatment and on knowing which symptoms have the greatest impact on a patient’s functioning. Despite the fact that accurate symptom profiles are critical for establishing effective symptom management, there is little empirical longitudinal research on multiple-symptom development in patients undergoing aggressive cancer treatment. A variety of important questions remain unanswered: How do clusters of symptoms vary during the course of treatment, particularly in a cohort of patients with the same diagnosis receiving the same treatment? How may one explain such variation on a mechanistic basis? Do physical and psychological symptoms interfere with the patient’s daily life in similar ways?

Symptom Burden in Cancer Survivors

To date, much symptom research has taken place in patients with advanced cancer during palliative care and end-of-life care. In large part because of the success of modern cancer therapies, the symptom burden experienced by patients is increasingly relevant as more and more cancer survivors desire fully to regain their social and workplace roles while dealing with the long-term effects of treatment. Examples are persistent fatigue in breast cancer survivors and long-term graft-versus-host disease following bone marrow transplantation.

Pain and non-pain cancer symptoms often present simultaneously and may exacerbate each other

Breast cancer survivors with fatigue are more likely to report behavioral problems than controls without fatigue. Not only do behavioral problems co-occur with fatigue, but researchers have associated them with elevated serum levels of several markers, interleukin-1 receptor antagonist, soluble tumor necrosis factor receptor type II, and neopterin. (Neopterin, a byproduct of macrophage stimulation by interferon gamma, is used as a marker of cellular immune activation.) The research group later found increases in another inflammatory marker of innate immune response (the plasma-to-cellular interleukin-6 ratio) in the same group of breast cancer survivors with persistent fatigue.

Evolving Symptom Research Can Apply Lessons Learned from Pain Research

A model for understanding and decreasing the burden caused by multiple symptoms has been provided by the relatively mature studies of a single symptom, cancer pain. The science of symptom control has thus evolved from a focus on pain alone to the exploration of symptom clusters (two or more symptoms that co-vary in onset and severity), a true turning point in the field of cancer-related symptom research that may be exportable to other chronic diseases (such as rheumatoid arthritis and heart failure) and normal conditions (such as aging). The subjective nature of symptoms, however, has provided a challenge for mechanism-based research, including the evaluation of novel treatments or preventive measures. Further, the biological mechanisms that may cause or contribute to the emergence of symptoms or symptom clusters from cancer or cancer therapy are just beginning to be explored.

The Methodology of Subjective Measurement

The first important lesson to be drawn from pain research is that patient-reported outcomes (PROs) are critical for the development of effective symptom research. Recent progress in symptom measurement has been substantial, despite the subjective nature of many of PRO measurements and outcome variables, the poor fit between current biomedical models of disease and this type of health-related investigation, and the lack of statistical models that integrate “rough” self-report data.
and biological data. Self-reported symptoms are now recognized by the U.S. Food and Drug Administration (FDA) as legitimate primary outcome variables for clinical trials leading to the registration of new drugs or devices.\textsuperscript{20} Well-developed PRO pain assessment tools have been widely used in the clinic, in clinical trials, and in translational pain research, and pain PRO instruments have been recognized by the FDA as good models for measuring other symptoms. Indeed, a problem shared by the pain and symptom literatures is the proliferation of distinct PRO assessment instruments.\textsuperscript{6}

**Self-reported symptoms are now recognized as legitimate primary outcome variables for clinical trials leading to the registration of new drugs or devices**

A high degree of variability in the severity of symptom reports in the face of similar objective signs and biomarkers of disease is relatively commonplace in practice, and has been well described in studies that explore the links between non-cancer physical pathology (such as spine disease), pain intensity, and impairment of function. However, when multiple-symptom PROs (which may differ from more general quality-of-life measurements in that they focus only on symptoms in symptom interference) are used as endpoints in intervention trials, the subjective experience of symptoms in addition to pain can be made known and rated. For example, in a systematic review of 21 validated symptom assessment instruments,\textsuperscript{21} the M.D. Anderson Symptom Inventory (MDASI)\textsuperscript{22} was judged to be a useful multiple-symptom assessment instrument in terms of its flexibility, reliability, validity, ease of completion, and utility in clinical management. The development of the MDASI followed that of the Brief Pain Inventory, which assesses symptom severity and interference with various activities from the patient’s perspective.\textsuperscript{22,23} Some symptoms cluster with the same temporal pattern during cancer treatment,\textsuperscript{24} a pattern that may be captured by longitudinal multiple-symptom assessment of PRO data.

**Mechanism-Driven Interventions**

A second important lesson to be drawn from the recent evolution of the field of pain research is that distinct biological mechanisms may cause or contribute to the emergence of cancer-related or treatment-related symptoms and their clusters. Even a single symptom such as pain or fatigue is liable to be multifactorial in its etiology.\textsuperscript{25}

With the possible exception of depression,\textsuperscript{26,27} cancer-related symptoms such as cognitive impairment, fatigue, and sleep disturbance have rarely been studied from a mechanistic perspective. Rather, the study of these symptoms has consisted primarily of descriptive studies. A typical symptom epidemiology study identifies patients with one type of cancer at a specific stage, measures symptom severity along with demographic factors (e.g., age, sex, minority status) or clinical factors that might predict high levels of symptoms, and assesses functional status and mood using a global or health-related quality-of-life instrument. A typical clinical intervention trial examines the reduction in severity of a specific symptom, generally on an empirical and not a mechanistic basis.

The dysregulation of cytokines, agents that modulate the inflammatory consequences of both cancer and cancer therapies, is a promising cross-disciplinary area of investigation in the quest to identify possible biological mechanisms that produce symptoms. Characteristics of the evolving models of cytokine-induced “sickness behavior” in animals are strikingly similar to symptoms reported by cancer patients undergoing treatment, as we\textsuperscript{28,29} and others\textsuperscript{30,31} have suggested. Animal “sickness behavior” refers to a constellation of behavioral and physiological responses observed after administration of inflammatory agents or specific proinflammatory cytokines.\textsuperscript{32,33}

Other agents and targets may emerge as equally important for the prevention and control of symptom clusters. Such pathways include noninflammatory cytokines and other proteins such as erythropoietin and related compounds,\textsuperscript{34} cyclooxygenase inhibitors, endogenous opioids,\textsuperscript{35} osteoprotegerin and related regulators of bone metabolism for treatment of bone pain,\textsuperscript{36} and nerve growth factor as a neuroprotectant in both animal and human models of cancer therapy.\textsuperscript{37-40} Other agents, such as the statins, have shown some promise in relieving postoperative morbidity and symptoms and have sufficient anticancer activity to be considered for study.\textsuperscript{41}

Animal sickness behavior models suggest a direction for future symptom research. Careful description of cancer-related symptoms and correlation of these symptoms with clinical laboratory data, coupled with both laboratory and clinical research studies, should be complemented by animal and in vitro studies that examine potential mechanistic bases for symptoms and their control. If associations between biological factors and symptoms are established and specific mechanisms identified, there is the potential for managing symptoms according to their underlying mechanisms rather than empirically, such as with psychostimulants for fatigue or opioids for pain. Recent basic research on the mechanisms of cancer-related bone pain\textsuperscript{32,33} and cancer-treatment-related neuropathic pain\textsuperscript{42} heralds new ways to control or even prevent symptoms related to the disease or its treatment.

**Symptom Research: An Interdisciplinary Research Challenge**

The pace of developing new curative approaches to cancer has not been matched by new approaches directed at the symptom burden that cancer and its treatment impose. Because symptoms are complex biological and behavioral phenomena, understanding them requires integrative studies involving behavioral scientists, immunologists, neurocognitive and comparative neuroscientists, statistical modelers, and cancer clinicians, especially clinicians with expertise in performing clinical trials. Although progress has been made in some aspects of symptom research, the challenges to bringing together interdisciplinary translational research teams are substantial. Many disciplines that could contribute to understanding the pathogenesis of symptoms (for example, functional imaging) have not yet been engaged. The interdisciplinary field of symptom research
requires a long-term structural framework in which to apply and generalize the results of research in a way that cannot be achieved within individual disciplines. Such an approach might include merging behavioral and biological disciplines to clarify the mechanisms of symptom evolution, developing animal models that parallel the behaviors of patients with symptoms caused by cancer or its treatment, developing new statistical methods to integrate longitudinal symptom reports with multiple biological data points obtained during clinical studies, testing potential novel agents for symptom control in both preclinical studies and clinical trials, and employing experts in organizational structure and management to provide models and training to maximize the productivity of cross-disciplinary research.

Conclusion

The rich history of research into a single symptom, cancer pain, provides a model pathway for the study and alleviation of the burden caused by multiple symptoms. Implementation of this pathway, which includes epidemiology, basic and clinical research, advocacy, and practice change, provides a solid foundation for an interdisciplinary field of research on clusters of cancer-related symptoms. This growing field embodies the goal of the U.S. National Institutes of Health to foster and apply creative discoveries and innovative research strategies to advance our capacity to protect and improve health. However, the present reality is that research into the mechanisms of symptoms is difficult to conceptualize, organize, and fund. A recent search of funded U.S. federal grants (basic and clinical) for individual symptoms suggests little support for these investigations, even though relatively small increments in our basic and clinical knowledge base are likely to substantially improve care for very ill patients.10

Elevating secure enhanced funding will require that medical professionals and policymakers have a clearer and broader understanding of why cancer symptoms, including treatment-related ones, can be so distressing for patients and their families, and why debilitating symptoms may persist indefinitely as a result of the very same treatments that have cured the primary cancer. Just as has begun to occur for cancer pain control, symptom prevention and management are likely to improve once they are subjected to the same scientific rigor that has been applied to controlling cancer itself. This scientific rigor, for which there is urgent need, may be achieved by creation of clinical-academic professional career tracks with symptom control as a primary research goal, clinician education spanning patient-reported and biomedical measurements, and clinical trial design methods to translate preclinical insights into clinical investigation.

References


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