

Research Priorities in Geriatric Palliative Care: Nonpain Symptoms

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Abstract

Research addressing the burden, assessment, and management of nonpain symptoms associated with advanced illness in older adults is limited. While nonpain symptoms such as fatigue, sleep, dyspnea, anxiety, depression, cognitive impairment, nausea, and anorexia-cachexia are commonly noted by patients and clinicians, research quantifying their effects on quality of life, function, and other outcomes are lacking and there is scant evidence regarding management. Most available studies have focused on relatively narrow conditions (e.g., chemotherapy-induced nausea) and there are almost no data relevant to patients with multiple morbidities or multiple concurrent symptoms. Assessment and treatment of nonpain symptoms in older adults with serious illness and multiple comorbidities is compromised by the lack of data relevant to their care. Recommended research priorities address the documented high prevalence of distressing symptoms in older adults with serious illness, the unique needs of this population due to coexistence of multiple chronic conditions along with physiologic changes related to aging, the lack of evidence for effective pharmacologic and nonpharmacologic interventions, and the need for validated measures that are relevant across multiple care settings.

Outline of the Scope of the Problem

ADVANCEMENTS IN MEDICAL SCIENCE and health care have changed the nature of dying in the United States. Death is no longer predominately the sudden result of infection or injury, but is now more likely to occur slowly at older age, and at the end of a period of life-limiting or chronic illness. Patients over age 65 comprise 12% of the population in the United States but represent 60% of cancer patients.¹⁻³ The U.S. health care system also faces the challenge of caring for more older individuals with chronic, progressive medical illnesses such as heart failure (HF), end-stage renal disease (ESRD), and neurodegenerative illnesses such as Parkinson's Disease (PD) and Alzheimer's Disease (AD). These conditions frequently coexist. For example, up to one-third of elderly patients with ESRD have four or more chronic conditions⁴ and cancer also frequently coexists with multiple other comorbidities in older patients.⁵ Older adults with serious illness often have high symptom burden, complex treatment regimens, and fragile social support systems. While the number of reported symptoms correlates directly with age, elderly patients are less likely to report their symptoms as very distressing. Given that well over three-fourths of all individuals dying in the United States are aged 65 and older and that many have multiple chronic illnesses, the difficulty in addressing their needs effectively will only increase with time.⁶⁻⁹

Despite the need for relevant research addressing these issues, the elderly are underrepresented in trials compared to the real world, and age-specific trials are limited. Studies show that one in five trials excluded patients because of age, and nearly half of the remainder included criteria that made participation by older subjects less likely, including presence of chronic or other conditions unrelated to the primary focus of the trial. The combined result is a shortfall in evidence to inform the optimal treatment of older patients, particularly those with multiple chronic conditions or serious or advanced illness.¹⁰⁻¹⁵ Appropriate guidelines that focus on symptom management in this population are inadequate for almost all common symptoms other than pain.¹ The lack of data in the elderly necessitates use of clinical judgment for individual patients. To provide optimal care for this population, there is an urgent need for evidence to inform management of chronic illnesses and their consequent physical, social, and psychological burden; and coordination of complex medical care.

Summary of the Current Evidence

Among studies that have documented prevalence, the most common nonpain symptoms in older adults with serious illness are fatigue, sleep disturbances, dyspnea, depression, anxiety, cognitive impairment, constipation, nausea, and anorexia-cachexia, with most patients experiencing multiple

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Accepted April 1, 2013.

concurrent symptoms.¹⁶ These symptoms are among the primary determinants of health-related quality of life and function across numerous conditions.^{17,18} Given that the distribution and impact of nonpain symptoms may differ between younger and older patients, age-specific research is critical to guiding symptom assessment and management in older adults.¹⁹ Data that do exist are primarily descriptive studies in cancer patients or in single morbidities, such as HF, ESRD, PD or dementia, with little evidence to inform symptom management among older adults with serious illness, especially with comorbidities. Existing literature finds that symptoms are often undertreated in older patients with serious illness, particularly in long-term care settings.^{20–27}

a) Fatigue, dyspnea, and sleep disturbances

Symptoms of fatigue, dyspnea, and sleep disturbances (including both insomnia and hypersomnolence) are significantly elevated among individuals with cancer, ESRD, HF, and PD compared to healthy older adults.^{28–31} For example, fatigue is experienced by 60%–97% of ESRD patients;³² dyspnea is reported by over three-fourths of older adults with advanced HF;³³ and 40%–90% of PD patients report sleep disturbances. These symptoms are consistently correlated with poor quality of life and may be more common in older adults than younger individuals with the same disease. For instance, fatigue appears to be more common in older than younger hospitalized cancer patients.³⁴ Potential mechanisms of these symptoms include exacerbation of age-related decreases in muscle strength and mass; medication side effects (e.g., antineoplastic agents);³⁵ cardiovascular dysfunction and pulmonary edema (e.g., HF); anemia (e.g., ESRD);³⁶ and central nervous system dysfunction (e.g., PD).³⁷

Assessment of fatigue, dyspnea, and sleep disorders in older adults with serious illness is complex. Although there are numerous scales available for assessing fatigue, few have been specifically validated in elderly patients with advanced or comorbid illness.³⁸ Furthermore, in evaluating fatigue, it is important to distinguish between fatigue complaints and objective fatigability.³⁷ Older adults may limit their activities to avoid sensations of fatigue and thus have low scores on fatigue scales despite fatigue having a high impact on their function.³⁹ Similar concerns arise regarding the assessment of sleep dysfunction where several scales are available, but few have been validated in older adults with advanced illness.⁴⁰ Diagnosing sleep disorders as opposed to measuring sleepiness is particularly important where specific sleep pathologies (e.g., sleep apnea) may be seen in a population (e.g., ESRD) and indicate specific treatment.³¹ While both visual and verbal numeric dyspnea assessment scales have been validated in elderly adults,⁴¹ depression and anxiety are significantly correlated with the degree of dyspnea, and their relative roles are poorly understood.⁴²

There are limited existing data to guide management of these symptoms, with the exception of opioids for dyspnea in advanced cancer.⁴³ There is some evidence from studies of management of sleep disorders in general populations (e.g., treatment of specific sleep pathologies) but no studies specific to older adults with life-limiting or multiple chronic conditions. While stimulants are frequently prescribed for fatigue in patients with organ failure, cancer, and neurologic illness, there are no convincing studies to support this practice and

several negative trials.⁴⁴ A literature review published in 2009 identified 19 controlled trials of methylphenidate in medically ill older adults or in palliative care; conflicting results, small sample size, and poor methodologic quality limit the ability to make inferences regarding efficacy.⁴⁵ There is some evidence in older adults with cancer that exercise may be beneficial for fatigue.⁴⁶ Many studies have demonstrated that even in older adults, mean dyspnea scores improve with use of opioid agents while physiological measurements of respiration are largely unaffected.⁴⁷ Many providers are nonetheless hesitant to use opioids in older adults, citing polypharmacy and multiple comorbidities.⁴⁸

b) Depression, anxiety, and grief

Mood disorders including depression, anxiety, and anticipatory grief are common in older adults with advanced illness and are correlated with both poor quality of life and mortality. Depression increased all-cause mortality by 20% in elderly patients with HF;⁴⁹ anxiety disorders are present in up to 40% of PD patients, substantially adversely affecting quality of life.⁵⁰ Mood disorders are frequently underrecognized and undertreated in these populations, due in part to lack of adequate assessment tools, differences in presentations of mood disorders in these populations, and a failure of primary treating physicians to evaluate psychiatric issues.⁵¹ Anticipatory grief, or feelings of loss associated with current and future changes related to illness, is important to distinguish from depression, as it may have different causes and merit different treatment.⁵²

Numerous scales are available for assessing symptoms of depression and anxiety, many of which have been validated in older adults, including patients with cognitive impairment and dementia.⁵³ However, none of these scales have been validated specifically in the setting of serious illness, with many scales including items that may be due to the underlying medical disease instead of depression (e.g., fatigue, slowness).⁵⁴ Assessment of anticipatory grief using the Prolonged Grief 12-item questionnaire (PG-12), which is validated in cancer patients (not specifically elderly), can distinguish depression from grief.⁵²

Although management of depression in older adults with advanced illness typically parallels treatment in other populations, there are few studies to support this practice. Notably, in older adults with cancer and major depression, randomization to primary care based depression assessment and treatment improved not only depressive symptoms but also mortality in patients with depression.⁵⁵ However, among patients with dementia, randomization to two standard antidepressants (sertraline and mirtazapine) appeared to increase adverse effects versus placebo and did not improve depressive symptoms.⁵⁶

c) Nausea, vomiting, anorexia-cachexia, constipation, and other gastrointestinal symptoms

Gastrointestinal symptoms such as nausea, vomiting, constipation, mucositis, and anorexia-cachexia are common in patients with advanced illness and can cause substantial psychological and physical distress for both patients and their families. One study of cancer patients found that constipation may be more common in older patients.⁵⁷ The risk of mucositis in cancer patients increases with age and is associated

with decreased nutrition, as well as preexisting periodontal disease.¹ Vomiting, constipation, and cachexia may be easily assessed and diagnosed, but other gastrointestinal symptoms such as nausea lack assessment tools validated in older patients. Treatment of these conditions typically varies according to the underlying etiology. In cases where pharmacologic management is the only remedy, there are limited data to guide treatment. No standard for antiemetic therapy in the elderly has been established, and comparative data on the use of antiemetics in older patients is limited. There is little or no evidence guiding treatment of cancer-related anorexia and cachexia in older patients.

d) Cognitive dysfunction, delirium, agitation and hallucinations

Cognitive impairment is a defining feature of dementias such as AD, and is also common in other neurologic illnesses such as PD, as well as in cancer and end-stage organ disease.⁵⁸⁻⁶⁰ Cognitive impairment is a significant predictor of functional impairment and mortality. For example, up to two-thirds of ESRD patients experience cognitive impairment and cognitive impairment, is associated with a 46% increased hazard of death.^{61,62} While frequently associated with cognitive impairment, delirium, hallucinations, and agitation are distinct symptoms which are associated with significant patient and caregiver distress.⁶³ Delirium is one of the most common indications for use of palliative sedation.⁶⁴

Assessment of cognition in older adults may be accomplished through brief screening measures, such as the Mini Mental Status Examination (MMSE)⁶⁵ or Montreal Cognitive Assessment (MOCA)⁶⁶ or through more extensive formal neuropsychological testing. Although not specifically validated in older adults or in the setting of multiple morbidities, there are a few scales that have been developed and validated for the assessment of delirium in advanced cancer.⁶⁷ The Neuropsychiatric Inventory has been validated in neurologic populations for the assessment of agitation, hallucinations, and other common symptoms but has not been used in cancer or other medical conditions.⁶⁸ While less widely used, there are other scales for assessing agitation that have been applied to cancer patients (not specifically elderly).⁶⁹ There are few specific scales for assessing hallucinations outside of psychiatric populations.^{69,70}

Evidence for the treatment of cognitive dysfunction is varied, even for AD where it has been most thoroughly studied.⁷¹ Evaluation of potentially reversible causes of delirium or agitation such as urinary tract infection, pneumonia, or untreated pain is indicated.^{72,73} Management of delirium not due to other causes has been most studied in dementia, with mixed results even for widely used antipsychotics.⁷⁴ More recent studies have suggested that nonpharmacological approaches, including music therapy, may be effective in dementia; but there are no studies to provide guidance for older individuals with other diagnoses.⁷⁵

Outline of Knowledge Gaps

a) Pathophysiology

Effective assessment and treatment of nonpain systems in older adults requires an improved understanding of the pathophysiology of symptoms as well as the effect increasing age has on symptom perception. To use fatigue as an example,

research needs to define the phenomenology (e.g., distinguishing fatigue from dyspnea and sleepiness), determining the extent to which secondary causes contribute to fatigue (e.g., anemia, medications, sleep deprivation).⁴⁸ In addition, research is needed to understand contributions of the underlying disease to fatigue through, for example, inflammatory or metabolic mechanisms. How advanced illnesses produce this symptom as a primary manifestation of disease including inflammatory, metabolic, and neurologic involvement. Changes in aging physiology may alter perception, characteristic, and intensity of nonpain symptoms.⁴⁹ Understanding the relationship between aging physiology and symptom perception will inform effective symptom assessment and treatment.

b) Relationship to quality of life (QOL), disability, and prognosis

While there is a fair evidence base to suggest that nonpain symptoms are common and have a negative effect on quality of life, functional status, and prognosis, the data are largely descriptive, diagnosis specific, and lack information specific to the geriatric population. Deeper understanding of the relationship between nonpain symptoms and patient experience and outcomes requires moving beyond cross-sectional descriptive to prospective studies. For example, longitudinal observation of older cancer patients could help establish whether fatigue is itself a cause of functional dependence and if dependence could be avoided by treatment and prevention of fatigue.

c) Measurement

Despite the observation that older patients perceive and report symptoms differently than younger patients, older patients have largely been ignored in the validation of measurement tools for nonpain symptoms in the setting of serious illness. While development of measurement instruments relevant to this population has improved, further development and validation is necessary. Common standards for outcome measures and for how they are reported is essential to ensuring future success in comparing and synthesizing the literature.⁷⁹ Where validated symptom scales exist, they should be expanded and tested to extend to older patients with serious illnesses and multiple chronic conditions. Instruments should be constructed so that comparability across care settings, populations, and clinical conditions is possible. For example, while the Patient Outcomes Measurement Information System (PROMIS[®]) toolset provides a comprehensive library of measurement tools, most have not been studied in patients with cognitive impairment or in older patients with multiple comorbidities.^{21,80,81}

d) Management

There is a significant paucity of data with regards to treatment of nonpain symptoms in the geriatric population, especially those with multiple chronic conditions. The scarcity of data results in a dearth of specific recommendations or guidelines regarding drug selection, dosing, and side effects that account for changes in aging physiology, pharmacokinetics, and idiosyncratic reactions. With aging, an individual's organ reserve decreases, comorbidities develop, and functional status is affected. Management of symptoms in this setting requires knowledge of the biology of aging, and how aging systems interact with the symptoms to produce unique

situations in older adults. Even less is known about the possible interactions between symptoms and the effect these interactions may have on the patient, or how to best manage the presence of multiple distressing symptoms in the older individual with multiple chronic conditions. There are also very limited data about nonpharmacologic nonpain symptom management specific to this population.

Summary of Research Priorities and Proposed Studies

Given the documented high prevalence of distressing symptoms in older adults with serious illness, the unique needs of this population due to coexistence of multiple chronic conditions along with physiologic changes related to aging, the lack of evidence for effective pharmacologic and nonpharmacologic interventions, and the need for validated measures that are relevant across multiple care settings, the following are recommendations for research priorities for the next 5 to 10 years (see Table 1):

1. Studies that document the impact of nonpain symptoms and the presence of multiple symptoms simultaneously on quality of life, functional status, disease outcomes, and decision making in older patient populations with multiple comorbidities.
2. Conduct of comparative effectiveness studies and pragmatic trials, in addition to traditional randomized clinical trials, to study pharmacologic and nonpharmacologic approaches to managing nonpain symptoms in this population. Achieving this goal will require building better clinical and administrative data systems to facilitate this research, including development of improved billing and coding practices and use of new sources of data such as smartphone applications to better capture real-time symptoms. Such studies should document the relative benefits versus harms of treating, including implications in terms of polypharmacy and in the context of physiologic aging. In addition, studies are needed that identify individual variation in symptom presentation to enhance clinicians' ability to effectively and efficiently manage symptoms.
3. Systematic cataloguing and evaluation of the characteristics and relevance to geriatric palliative care of existing symptom assessment tools. Where possible, existing tools should be validated, rather than creating new instruments. Validated tools should be integrated into clinical data systems to enhance data capture and facilitate conduct of comparative effectiveness studies.

TABLE 1. RECOMMENDATIONS FOR RESEARCH PRIORITIES

<i>Research priority</i>	<i>Study objective</i>	<i>Study setting</i>	<i>Sample</i>	<i>Study design</i>
Understand the association between multiple symptoms and patient outcomes	To describe the impact of nonpain symptoms, especially the presence of multiple symptoms simultaneously, on quality of life, functional status, disease outcomes, and decision making.	Older adults with multiple chronic conditions.	Large	Longitudinal cohort, following participants across care settings and the disease trajectory.
Study pharmacologic and nonpharmacologic approaches to managing nonpain symptoms	To document the relative benefits vs. harms of treating, including implications in terms of polypharmacy and in the context of physiologic aging.	Older adults with symptomatic chronic illnesses receiving therapies aimed at alleviating symptoms.	Large	Comparative effectiveness research using existing clinical databases or pragmatic clinical trials of different therapeutic approaches in real world settings.
Study pharmacologic and nonpharmacologic approaches to managing nonpain symptoms, identifying individual variation.	To identify individual variation to enhance clinicians' ability to effectively and efficiently manage symptoms.	Older adults with symptomatic chronic illnesses receiving therapies aimed at alleviating symptoms.	Large	Secondary analysis of existing trial data or comparative effectiveness research using existing clinical databases.
Validation of symptom assessment instruments.	To validate symptom assessment instruments in the setting of multiple chronic conditions and multiple simultaneous symptoms.	Older adults with symptomatic chronic illnesses.	Medium	Measurement instrument validation, confirming psychometric properties.
Study of the most effective ways to integrate evidence regarding symptom management into practice.	To demonstrate the most effective means of integrating evidence-based constipation management across the care continuum.	Older adults with chronic illness and constipation.	Medium	Implementation science.

When possible, common tools should be utilized across studies to enhance comparison of data across studies.

4. Investigators (and grant reviewers) should think beyond the usual research paradigm of narrowly defined populations to embrace the complexity inherent in studying issues of relevance to an older population, planning for this complexity throughout the research process, from study design through analysis, interpretation, and dissemination/implementation.
5. Increased application of implementation science methodologies that study the most effective ways integrate evidence regarding effective symptom management into practice.⁸²
6. Development of interinstitutional and interdisciplinary relationships that enable access to resource-rich database networks for relevant research. Examples include use of data from the Veterans Administration (VA), Alzheimers Disease Research Centers (ADRC), National Alzheimer's Project Act (NAPA), and the Health and Retirement Study (HRS). In addition to helping realize many of the above research goals, these types of collaborations will also help ensure that research networks are incorporating outcomes that are important to all aspects of palliative care research.
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Acknowledgments

This work was supported by the National Institute on Aging (NIA) Claude D. Pepper Older Americans Independence Center at the Icahn School of Medicine at Mount Sinai [5P30AG028741].

Author Disclosure Statement

No competing financial interests exist.

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