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The challenges of symptom management for patients with multimorbidity in research and practice: a thematic review

Laura A. Petrillo, MD^{1,2} and Christine S. Ritchie, MD, MSPH, FACP, FAAHPM²

¹San Francisco Veterans Affairs Medical Center, San Francisco, California

²Division of Geriatrics, University of California at San Francisco, San Francisco, California

Abstract

Multimorbidity, the presence of multiple coexisting diseases or conditions, afflicts the majority of older adults, and is associated with increased mortality and healthcare utilization. In addition, multimorbidity negatively impacts quality of life and increases symptom burden. Yet, there is a dearth of evidence on how to best manage symptoms in patients with multimorbidity. Research in this area has been hampered by inconsistent definitions of multimorbidity and challenges in outcome measurement. Investigations of symptom management strategies in specific disease states, like cancer, typically exclude medically complex patients. In the absence of evidence, the American Geriatrics Society's recommendations for the care of adults with multimorbidity provide a useful starting point for clinicians. We present a case to demonstrate how the AGS recommendations can be tailored to the situation of symptom management in patients with multimorbidity. We also present suggestions for future research directions.

Keywords

Multimorbidity; Symptom Management; Palliative care

Introduction

Though medical practice has traditionally focused on the diagnosis and treatment of individual diseases, adults are frequently burdened by more than one illness or condition, particularly as they age¹. The negative effect of multiple comorbid illnesses on health is not simply additive; diseases compound each other, leading to medication-related problems², functional impairment³, and negative impact on health-related quality of life⁴. The concept of multimorbidity, defined by Boyd et al as “the total burden of biological dysfunction or physiologic dysregulation,”⁵ captures this problem, and a growing body of literature has accumulated in the past decade to characterize the population of patients with multimorbidity.

Corresponding author: Laura Petrillo, laura.petrillo@ucsf.edu.

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Many studies have examined the prevalence of multimorbidity⁶, as well as the impact of multimorbidity on health outcomes such as hospital admission⁷ or death⁸, and on system outcomes, like healthcare utilization⁹. As methodology to assess prevalence has varied across studies, estimates range widely, but the Centers for Medicare and Medicaid Services reported in 2012 that about two thirds of Medicare beneficiaries have 2 chronic conditions¹⁰. A more recent study in the US Veterans Administration found that 29% of US veterans have 3 chronic conditions, while 9% have 5 chronic conditions⁹. A systematic review of studies done worldwide to describe multimorbidity prevalence found that before age 40 approximately 20% or less of primary care patients had 2 diseases, with an increase in multimorbidity incidence throughout middle age and a plateau at 75% among patients around 70 years of age⁶.

Important efforts have been made to explore patient perspectives on living with multimorbidity¹¹, and to examine the symptom burden experienced by patients with multimorbidity, though more research is needed¹². A prospective study tracking older patients in their last years of life demonstrated that the prevalence of symptoms that restricted activity or function was higher in patients with multimorbidity than in those with zero or one disease, suggesting that multimorbidity negatively impacts not only length, but also quality of life.¹³

Despite the appreciation that multimorbidity is a common problem in the aging population, and affects health-related quality of life and symptom burden, there is a dearth of evidence on how to manage symptoms in patients with multimorbidity. Among the symptom-focused studies done in patients with advanced illness and at the end of life, the most evidence exists for management of pain, and to a lesser degree, dyspnea, in cancer. There is a paucity of evidence for how to manage pain, dyspnea or depression in non-cancer illnesses, let alone in patients with combinations of diseases or conditions¹⁴. We will herein describe the challenges that hinder efforts to study symptom management in multimorbidity, and with a case, suggest ideas for approaching symptom management in patients with multimorbidity.

Challenges in multimorbidity symptom management research

The first hurdle in studying multimorbidity is to consistently define it, as there is heterogeneity in the criteria defining multimorbidity in epidemiologic research on multimorbidity to date. The most basic, working definition is the presence of 2 diseases, though some investigators have also evaluated for the presence of dyads or triads of diseases. The question of whether medical diagnoses should exclusively be counted in the morbidity tally, or if conditions, like sensory and functional impairments or symptoms, like chronic pain, should be included, creates more ambiguity in the definition.

Tools like the Charlson Comorbidity Index and the Cumulative Illness Rating Scale (CIRS) have been used to measure burden of multimorbidity in research studies, primarily to adjust for the impact of multimorbidity on mortality. The Functional Comorbidity Index (FCI) was developed with health-related quality of life as an outcome,¹⁵ though in a comparison study of the Charlson, the CIRS and the FCI, the CIRS explained the most variation in health-related quality of life when validated against the SF-36 questionnaire¹⁶. These indices of

disease burden are all distinct from measures of acute illness severity such as the Acute Physiology and Chronic Health Evaluation II (APACHE II) score, a clinical tool that uses physiologic markers, comorbidity and other factors to predict hospital death¹⁷.

Another reason that minimal data exist about patients with multimorbidity is that most research studies that are focused on single diseases exclude patients with significant comorbid conditions¹⁸. By definition, patients with multimorbidity are complex and diverse, but it is exactly that complexity that is unattractive in research studies, which aim to isolate the effect of one variable, or select a population with the best likelihood of response to a treatment (and lowest likelihood of harm). Comorbidity indices like the Charlson do not capture the diversity or range of symptom severity caused by the illnesses of which they are comprised, and also do not take into account mental illnesses, which can detract significantly from quality of life¹⁹. Heterogeneity in the population of multimorbidity patients also affects the generalizability of study findings.

There are many challenges inherent in measurement of symptoms in patients with multimorbidity. Tools used for rating symptoms are not validated for patients with multimorbidity. In particular, depression is difficult to identify in patients with multimorbidity, as somatic symptoms of depression can be hard to distinguish from symptoms of other chronic illness²⁰. Another challenge of symptom management research in the context of multiple conditions relates to the dynamic nature of symptoms and the difficulty of capturing the patient's symptom experience when assessment intervals are often infrequent, and assessments do not fully capture the multiple factors (and conditions) influencing symptoms at any one time¹².

In addition to the need for inclusion of patients with multimorbidity into treatment trials, more data about how to prognosticate for patients with multiple conditions is necessary to guide treatment choices and eventually, the timing of a shift in focus to predominantly symptom-focused care²¹. Other important future research directions include better understanding of the relationship between symptom burden and quality of life in patients with multimorbidity, as well as how to best apply shared decision-making to the complex risk-benefit calculus in patients with multimorbidity.

Ideas for approaching symptom management in patients with multimorbidity

Though the evidence is sparse, and no guidelines yet exist for the care of patients with multimorbidity, the American Geriatrics Society (AGS) has put forth a general approach to the overall care of older adults with multimorbidity²² that we will draw on and supplement to suggest an approach to symptom management in these patients. A modified schema of the steps in the AGS guiding principles are presented in Figure 1. Though these are arguably important steps in any patient-centered encounter, they are nevertheless valuable considerations for patients with multimorbidity. To illustrate these ideas in action, we present the case of Barbara, a patient with multiple comorbid conditions seen in an outpatient palliative care clinic. Each step of the case represents a step from the AGS guiding principles.

Case: Barbara is a 55 year-old woman with history of Stage II ovarian cancer, diabetes and depression. She underwent surgery and has completed adjuvant treatment with carboplatin and paclitaxel, and has had no evidence of disease for two years. Her diabetes is poorly controlled, however, and she experiences persistent depressed mood despite counseling and treatment with a selective serotonin reuptake inhibitor (SSRI). She is referred to outpatient palliative care for symptom management. At her first clinic visit, she says that she is bothered most by burning, numbness and tingling in her hands and feet.

Step one: Learn about patient concerns and preferences

In symptom management, more so than any other aspect of medicine, the patient experience is the major focus and driver of treatment choices, and patients dictate the self-administration of as-needed medications. Thus, close collaboration between patients and their healthcare providers in treatment decisions is critical. A long-term qualitative study by Morris et al. suggests that patients with multimorbidity are constantly reassessing their prioritization of conditions, as they shift between experiencing disruption by the condition and finding the ability to accommodate to the condition's challenges²³. Physicians often approach problem lists sequentially, and can be slower to appreciate the dynamic nature of the patient experience.

Prior to delving into a discussion of the possible treatment choices to address patient complaints, it is beneficial to have a sense of the patient's values and approach to his or her own health. Fried et al demonstrated that patients felt comfortable prioritizing broad health outcomes, such as "keeping me alive" versus "maintaining independence" and "reducing pain and other symptoms," and suggested using these questions to open conversations with patients about goals and preferences²⁴. Inquiring about values and goals prior to presenting options can avoid overwhelming patients with extensive discussion of options that are unlikely to meet their treatment goals and allow providers to make a patient-centered recommendation.

To determine the best course of action for Barbara, her palliative care doctor asked about Barbara's goals of treatment. Barbara felt that her pain was so bothersome that minimizing the discomfort she feels is her top priority. Pain interferes with her sleep, and she hopes that relief from pain will also allow her to get back to work. She does not mind taking medications more than once during the day if it might help, and is willing to chance side effects, like sedation, if she can get relief. She has concerns about the cost of any proposed treatment.

Step two: Interpret the evidence for potential interventions

As described above, the evidence is lacking for symptom management in general, and for patients with multimorbidity in particular. Nevertheless, the existing literature can serve as a starting point for evaluating possible therapies. In examining the evidence for a proposed treatment in a single disease or condition, an important first step is to critically evaluate the methods, specifically the inclusion/exclusion criteria, as well as study design. Randomized clinical trials are the gold standard but are often most stringent in patient selection and thus least generalizable to patients with multimorbidity. Any benefits seen should be cautiously

interpreted and weighed against the risk of harm, ideally reported as changes in absolute risk so that number needed to treat and number needed to harm may be calculated²².

Barbara agrees to a trial of gabapentin for neuropathic pain, suggested by her palliative care doctor on the basis of a recent meta-analysis of gabapentin in chronic neuropathic pain that demonstrated that 43% of patients can expect at least modest benefit from gabapentin, while there was an absolute difference of 0.15 in the proportion of patients reporting adverse events from gabapentin over placebo, leading to a number need to harm (NNH) of 6.6²⁵.

If available, a very relevant metric for patients with multimorbidity is the time to benefit (or harm) from an intervention¹⁸. The most classic examples of delayed time to benefit are cancer screening, or preventive medicine like statins for elevated cholesterol or tight glucose management in diabetes. In symptom management, with the exception of medications like antidepressants that need to be increased slowly to therapeutic dose, effects of medications are usually immediate, so time to benefit is less relevant. However, in patients with limited prognosis, the calculus regarding time to harm may shift, and treatments that are less acceptable in patients with a long life expectancy, like opioids for chronic pain because of risk of dependence, may be more reasonable to consider.

Another important consideration in patients with multimorbidity is medication interactions. Not only should clinicians consider the effect of one drug on the metabolism of another, but in addition, expected side effects of one medication may make the experience of another condition worse¹², such as corticosteroids used for a COPD flare potentiating underlying psychotic illness or complicating glucose control in diabetes. The lack of care coordination between the many subspecialist providers who serve patients with multimorbidity also contributes to medication complications². The US Department of Health and Human Services has therefore identified care coordination as a top priority in a strategic framework to improve the care of patients with multimorbidity²⁶.

Step three: Address prognosis

A patient's ability to make informed decisions is predicated on her understanding of her medical conditions, including prognosis. For patients with cancer and comorbid conditions, survival estimates based on outcomes from treatment trials over-estimate survival benefits for the overall population of cancer patients, because of strict exclusion criteria that selects against cancer patients with poor performance status²⁷. Though disease-specific information is a useful starting point, this strong caveat, that patients with comorbid conditions and decreased functional status live less long than patients who are fit enough for trials, should be taken into consideration in discussions of prognosis. Outside of cancer, non-disease-specific prognostic tools are largely driven by functional status²⁸, and therefore this may be a more relevant factor in prognosis estimation. These tools are synthesized into an accessible user interface on the website eprognosis.ucsf.edu, which allows providers to choose a prognostic tool tailored to the patient's clinical setting.

For patients with multimorbidity, the end of life can be difficult to recognize, but the Palliative Performance Scale (PPS)²⁹, a particular functional based prognostic tool developed for use in hospice patients, may be most useful for that purpose. A study by

Wharton et al found that the PPS is highly predictive of mortality in an outpatient home-based primary care practice, and therefore identified patients for whom palliative care consultation (and thus increased attention to symptom management) may be beneficial³⁰. Another study of inpatients referred to palliative care consultation in Singapore found that change in PPS was highly predictive of mortality³¹.

Discussion of prognosis is always challenging, but providers with the luxury of a long relationship with a patient, like primary care doctors and outpatient primary care and palliative care doctors, can “cultivate prognostic awareness” over time by following patient cues about readiness to receive information³². Communication experts Anthony Back and Robert Arnold provided the following recommendations for oncologists, though they are useful for any provider approaching a prognosis conversation: first gauge how much patients want to know about prognosis prior to sharing the information, then acknowledge patient emotions in reaction to the news and check for understanding³³. The website eprognosis.ucsf.edu also has a series of videos demonstrating how to individualize counseling about prognosis for patients.

Step four: Consider feasibility of treatment

Case: Barbara returned to clinic and reported that the burning pain in her hands and feet had improved on gabapentin, despite feeling a little sleepier at times. However, on a subsequent visit, she mentioned that sensation in her feet was diminished, and she had fallen a few times at home. She also admitted to drinking wine on occasion to deal with her stress, and shared that taking pills three times a day was difficult. The palliative care pharmacist suggested consolidating her antidepressant and neuropathic pain regimen into monotherapy with a serotonin-norepinephrine reuptake inhibitor (SNRI), which may have benefit for both depression and neuropathic pain. After discussion of the risks and benefits, Barbara agreed to taper off gabapentin and switch to an SNRI.

In addition to the potential harms of a proposed treatment, it is important to consider the burden of any proposed therapy. In this context, the concept of burden encompasses not only the financial cost, but also the inconvenience incurred by a complex treatment option. In a qualitative study, Eton and colleagues explored the experience of patients with multiple chronic conditions who were enrolled in a pharmacist-led medication therapy management program. They found that patients felt burdened by the work of self-care, particularly the time-consuming nature of adhering to medication regimens and clinic appointments, as well as remaining vigilant about their health, and staying abreast of new research and treatment options³⁴.

In the case presented above, both the harms of treatment (sedation from gabapentin increasing risk of falls) and the feasibility of treatment (the necessity of thrice daily pill administration) prompted re-evaluation of Barbara’s neuropathic pain regimen and rotation to an alternative treatment. Though her primary objective, relief from pain, had been met by the medication, the new risks and burdens were too great to justify its continuation.

Step five: Optimize therapy

In summary, choosing the optimal therapy for a symptomatic complaint of patient with multimorbidity involves first considering patient preferences and priorities, then matching treatments suggested by the evidence with those preferences, counterbalanced against the possible harms and burdens of treatments. As results can be unpredictable, it is important to build into any treatment plan a timeline and set of parameters for assessing response to treatment, and have flexibility to try something different if the first treatment is unsuccessful by predetermined metrics. Setting realistic expectations on which providers and patients can agree prior to initiating therapy maximizes likelihood of successful treatment. In addition, clinicians should consider whether medications can be discontinued as a routine part of the medication prescribing process at every patient encounter, to minimize risk of harm from adverse effects or drug-drug interactions, or simply to test whether medication is still needed.³⁵

Future directions

Future studies might evaluate the comparative effectiveness of symptom treatments in complex patients who might otherwise be excluded from research^{18,36}. An idea with potential for studying patients with multimorbidity is the concept of an “N-of-1 trial,” in which treatments are randomly allocated and assessed in a single subject using objective criteria, and the patient serves as his own control³⁷. Given that it would take an enormous amount of resources to test the benefits (and harms and feasibility) of every treatment in every complex patient, N-of-1 trials are more efficient, if performed rigorously, and can be combined into meta-analyses that offer population-level insight.

Conclusion

Multimorbidity is an incredibly common and overlooked problem in our healthcare system, and only stands to increase in relevance as patients live longer and have the opportunity to accrue a greater burden of chronic illness. At present, there is a dearth of evidence about how to manage symptoms in patients with multimorbidity. However, as suggested by the American Geriatrics Society, a comprehensive approach to patients with multimorbidity includes focusing on patient preferences, carefully interpreting the available evidence (including both the benefits and potential harms), and thinking critically about the burden of any treatment, are important first steps. Taking time to elicit patient goals and preferences, and apprise patients of their prognosis if they want to know, are especially important in symptom management discussions with patients with multimorbidity. Another key is partnering with multidisciplinary team members, including pharmacists, nurses, social workers and other ancillary providers to create a comprehensive care plan that is safe, streamlined, and meets the dynamic needs of patients with multimorbidity.

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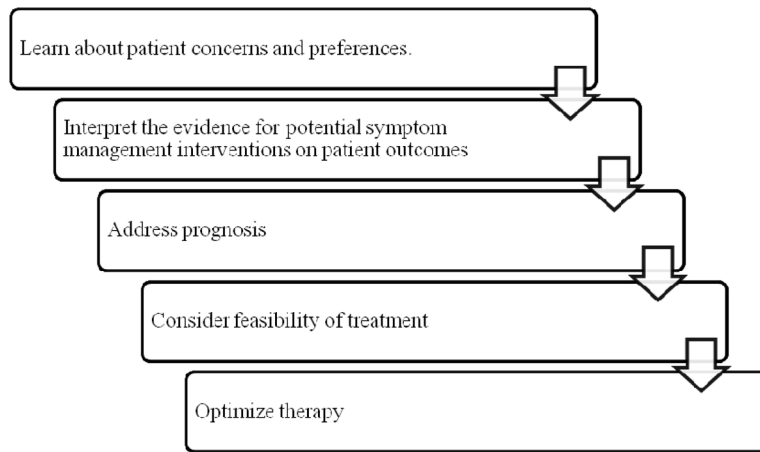


Figure 1. Approach to choosing symptom management therapy in patients with multimorbidity, adapted from American Geriatrics Society “Guiding Principles for Care of Older Adults with Multimorbidity”²²

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