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The Impact of Medication Use and Medical Morbidity on Symptom Burden in Older Patients

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Abstract

THE IMPACT OF MEDICATION USE AND MEDICAL MORBIDITY ON SYMPTOM BURDEN IN OLDER PATIENTS. Maria A. Han, Mary E. Tinetti, and Lisa M. Walke. Section of Geriatrics, Department of Internal Medicine, Yale University, School of Medicine, New Haven, CT.

Older patients suffer from a greater number of medical morbidities, consume a greater number of prescribed medications, and report lower levels of quality of life than their younger counterparts. The objectives of this study were to determine whether there is 1) an association between medical morbidity and symptom burden or 2) an association between medication use and symptom burden. This was a cross-sectional study of the symptoms, medical morbidities, and medications reported by 159 community-dwelling male patients 65 years of age or older. Correlations were drawn using linear regression analysis. On average, the participants in this study suffered from 2.56 +/- 1.36 medical morbidities, were prescribed 7.91+/- 2.83 medications, and reported 3.17 symptoms at any severity. The results of this study demonstrated a direct correlation between number of medical morbidities and symptom burden ($R^2 = 0.94$). Our study did not find a significant correlation between medication use and symptom burden ($R^2 = 0.20$). The findings of this study suggest that the number of medical morbidities has a stronger negative impact on symptom burden than the number of medications used. Thus, when attempting to improve quality of life for older patients, physicians should focus on the treatment and alleviations of symptoms associated with medical morbidity.

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Table of Contents

Introduction

It is worthwhile to secure the happiness of the patient as well as to prolong his life.
-- Dr. William J. Mayo, 1935

This quote highlights the responsibility of health care providers to offer medical services not only to prolong life, but also to improve the quality of life for their patients. The growth of sophisticated life-sustaining medical technology in the last century, combined with a greater focus on medical care at the end of life, has contributed to a longer life for many people in the United States. Whereas only one in 25 Americans reached age 65 in 1900, one in every eight Americans was at least 65 years old in 1990. This dramatic increase in life expectancy has been shown to be largely the result of a decline in mortality among middle-aged and elderly populations. For example, in 1900, a person aged 65 years could expect to live nearly 12 more years; while today, a 65-year-old person can expect to live more than 17 additional years (1).

Prolonging life, though, has not come without consequences. With increased longevity, chronic illnesses among older patients have become more prevalent and are now a major cause of death and disability in old age. In this light, the Council on Ethical and Judicial Affairs for the AMA has suggested that the increased attention being given to prolonging life may eventually result in insufficient attention to protecting the quality of life (2). This concern may be particularly relevant for older patients, who often report declining levels of quality of life with advancing age (3). In honoring the ideals articulated by William Mayo, future research should investigate how medicine can continue to foster an individual's quality of life as they age, particularly as they face the possibility of frailty and dependence.

I. Study Question

The literature shows that on average older persons report lower scores on various measures of quality of life compared with their younger counterparts (3). Quality of life (QOL), as a health outcome, can be most broadly defined as a multidimensional concept that refers to an individual's overall life satisfaction and total well-being (4). More specifically, the Center for Health Promotion at the University of Toronto has divided the QOL outcome into three broad domains: *well-being* (including physical, psychological, and spiritual components), *belonging* (including physical, social, and community components), and *becoming* (including growth, practical, and leisure components) (5). It is thought that these domains encompass the most important contributors to human well-being. Across these three domains, older persons on average report lower levels of satisfaction, resulting in reduced QOL scores.

Demonstrating this trend in QOL scores with age, a study conducted by Farquhar showed that the percentage of patients who report their quality of life as "very positive" decreased from 52 percent of those aged 65-85 to 37 percent of those aged over 85. Likewise, the percentage of patients who report their quality of life as "very negative" increased from six percent of those aged 65-85 to 25 percent of those aged over 85 (3). This decline in QOL with age may be driven by changes in any or all of the domains mentioned in the previous paragraph, and each of these potential determinants should eventually be explored in an endeavor to improve QOL. However, this particular study will focus solely on the role that physiologic determinants may have in declining QOL scores, as this is one important set of determinants which has been shown to be significantly affected by age. Multiple studies have demonstrated an increase in both

medical morbidity and medication use with age; thus, our study will investigate any associations that may exist between these two variables and QOL measures.

The older population in the United States suffers from a significantly greater number of medical morbidities than their younger counterparts. For example, a study conducted by Stephen Machlin for the Agency of Healthcare Research and Quality showed that the proportion of adults with at least one chronic condition increased dramatically with age, ranging from 36.4 percent of young adults age 18–34 to 91.5 percent of the elderly age 65 and over (6). Similarly, the proportion of persons with two or more chronic conditions also rose dramatically with age, ranging from only 14.4 percent of persons age 18–34 to 76.6 percent of the elderly age 65 and over. The results of this study demonstrate the physiologic deterioration that often accompanies the natural aging process.

As older patients suffer on average from a greater number of medical morbidities, they consequently utilize the health care system with greater frequency as well. For example, in 2006, those aged 65 years and older made up 38 percent of all hospital discharges and used 43 percent of the days of care in the inpatient setting (7). This age group also consumed over 30 percent of all prescription medications taken annually in 1997 (8). As a result of increased utilization and consumption, per person health care spending for the 65 and older population was $14,797 in 2004, which was 5.6 times higher than spending per child ($2,650 in 2004) and 3.3 times spending per working-age person ($4,511 in 2004) (7).

Given the significantly greater burden of both disease and treatment endured by older patients, it is important to quantify and monitor the overall effect that these medical

morbidities and medical treatments have on patient QOL. For example, it is quite possible that worsening QOL with age occurs simply as a result of age-related physiologic deterioration and the increased rates of chronic illness incurred by this population; however, as medical treatment itself can be associated with numerous side effects and complications, medical treatments may also be contributing to worsening levels of QOL in older patients.

The impact that medical treatment has on QOL should ideally be considered for all forms of patient therapy; however, we think that this consideration is particularly relevant regarding the use of pharmacotherapy in older persons, as pharmacotherapy is by far the most commonly used form of medical therapy in the United States (9). For example, Field et al. reported that 90% of patients aged 65 and older use at least one medication per week; more than 40% use five or more different medications per week, and 12% use 10 or more different medications (10). Given the widespread use of medication among senior patients, we chose to limit our study of medication treatment to the use of medication and its impact on QOL measures.

Previous attempts by investigators and clinicians to assess the impact that medical morbidity and medication use have on patients' lives have taken a number of forms, including measurement of Adverse Drug Reactions (ADRs), Health-Related Quality of Life (HRQOL), and Symptom Burden. Though each of these measures is fraught with its own limitations, each represents a valuable tool in assessing changes in the patient experience associated with changes in medication regimens and disease progression. These measures have allowed investigators and clinicians to quantify patient well-being. The next three sections will discuss the strengths and limitations of each of these

measures and will highlight the most important data collected to date regarding medication use and medical morbidity using each of them.

II. Adverse Drug Reaction (ADR)

Definition:

As physicians and pharmacists have become increasingly cognizant of the side effects associated with medical treatment, efforts have been made to quantify the negative impact that medication use may have on patient well-being. Recently, the clinical recording of ADRs has been used to directly measure the injurious effects of medication use.

The World Health Organization defines an ADR as "a response to a drug which is noxious and unintended and which occurs at doses normally used for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function (11)." ADRs have been most commonly documented by pharmaceutical companies in clinical drug trials, by hospitals in quality improvement projects, and by research investigators in clinical studies.

Findings:

One of the most significant findings identified regarding ADRs is their direct correlation with age. A meta-analysis of 68 observational studies reported that the proportion of admissions related to ADRs in older people was nearly four times higher than that in younger people (12). Specfically, a study conducted by Hurwitz showed that among patients aged over 60, 15.4 percent suffered an ADR compared with 6.3 percent of those aged under 60 (13). A similar study by Seidl et al. reported that 24 percent of

patients aged 81 or over suffered an ADR, compared to 16 percent of patients aged 50 or older and 11 percent of patients younger than 50 (14). These findings suggest that the risks associated with medication use increase as patients grow older.

Because virtually all medications have the potential to cause side effects and because older people consume a greater number of medications, the direct association between age and ADRs is not particularly surprising; however, the relationship between age and ADRs does not seem to solely depend upon the number of medications patients consume. Rather, the association between age and ADRs is speculated to be multifactorial in origin with other important contributors being age-related changes in pharmacokinetics/pharmacodynamics and the number of medical morbidities. A precise model for the interaction of these multiple factors in causing ADRs has not been established; however, there is data supporting the independent role of each, which will be discussed below.

The number of prescribed medications taken by a patient has emerged as an independent risk factor for ADRs in the older population. This is a clinically reasonable finding as there is increased opportunity for medication side-effects and drug-drug interactions when multiple medications are used. For example, Hutchinson et al. conducted a study of 1026 patients which suggested a direct correlation between increasing age and ADRs; however, when the study controlled for the number of prescribed medications, the association between age and ADRs was lost (15). In another study, Ghandi et al. showed that the addition of each new drug to a treatment regimen increased the risk of an ADR by 10% (16). Finally, a study by Agostini et al. demonstrated a linear relationship between number of prescribed medications and the

occurrence of two commonly reported ADRs, weight loss and impaired balance. This correlation persisted even after extensive adjustment for chronic medical illness (17).

In addition to a greater sheer number of medications taken by older patients, this patient population also demonstrates well-documented changes in drug clearance and drug sensitivity that occur as a result of the normal aging process. The four traditional components of pharmacokinetics are absorption, distribution, metabolism, and excretion. All components, except absorption, are significantly affected by age (18). For instance, distribution is affected by changes in body composition, as an age-related increase in body fat results in a greater volume of distribution for lipid soluble medications (19). Additionally, metabolism of drugs by the liver (20) and excretion of byproducts by the kidneys are often impaired in older patients (21). Coupled together, these physiologic changes prolong elimination half-life and necessitate alterations in medication dosing for elderly patients.

Finally, the number of medical morbidities suffered by a patient has also emerged as a potential risk factor for ADRs. As there is no clear definition of comorbidity or multimorbidity, the phrase ‘medical morbidity’ is used in this study to represent equally significant chronic conditions, rather than secondary diseases to a primary disease under examination (22). The association between medical morbidity and ADRs may exist because an increased number of medical morbidities increases vulnerability to ADRs by impairing body systems; for example, cardiovascular, pulmonary, renal, and hepatic insufficiencies can all cause changes in pharmacokinetics and pharmacodynamics, as was discussed above.

A study conducted by Zhang et al. demonstrated that the presence of medical morbidities, including congestive heart failure (CHF), diabetes, peripheral vascular disease, chronic obstructive pulmonary disease (COPD), and rheumatologic disease were all strong predictors of hospital readmissions for ADRs (12). Similarly, a number of studies have also considered the effect that medical morbidities has on the occurrence of adverse drug events (ADEs) such as falls and incontinence; ADEs can be thought of as the immediate sequelae of ADRs. For example, a study by Field et al. also showed that scores of five or higher on the Charlson Comorbidity Index were associated with increased risk of ADEs (10). All of the above studies suggest that medical morbidities may have an independent and dose-related effect on the occurrence of ADRs and ADEs in older patients. However, the association between morbidity and ADRs might also be explained by Berkson's bias—that is, that ADRs are more likely to be identified and diagnosed in this population because the presence of medical morbidities increases a person's contact with the health care system (12).

Limitations:

In summary, the occurrence of ADRs has been shown to be directly associated with age, medication use, and medical morbidities. However, while the occurrence of ADRs provides important information regarding the risks of medication use in older patients, there are significant limitations associated with estimating the ill-effects of medication use by simply measuring the frequency of ADRs. First, the vast majority of studies regarding ADRs in older patients have been conducted in the inpatient setting (23). The inpatient setting is a highly-regulated environment where health care workers determine when a patient begins, takes, and discontinues a specific medication. Health

care workers are also skilled at monitoring for and identifying ADRs, and hospitalized patients have repeated access to health care workers and ample opportunity to report symptoms. Identification of ADRs is much more challenging in the outpatient setting where a significant proportion of ADRs are suffered. In order for an ADR to be recorded in the outpatient setting, a patient needs to recognize a symptom, become bothered by that symptom, and choose to call their physician or go to the emergency department.

The challenge of identifying ADRs in the outpatient setting has been highlighted in multiple independent studies. In a study of ambulatory patients, Weingart et al. reported that outpatients discussed 196 (69 percent) of their 286 medication symptoms with their doctors. Twenty-three percent of these patients' unreported medication symptoms led to preventable or ameliorable ADRs, and one in five unreported symptoms resulted in an ADR that could have been prevented with medical assistance (24). Patients likely failed to report nearly one-third of their symptoms for multiple reasons. Many patients do not report ADRs because they do not recognize the events as drug reactions but rather attribute them to a disease process. It is also possible that mild or transient symptoms were not reported or that patients were uncomfortable discussing potentially embarrassing symptoms, such as diarrhea and impotence, with their physicians (25).

Second, in addition to difficulties in recording ADRs, using ADRs as a benchmark of patient well-being is also limited in that most records of ADRs do not take into account the severity of the medication reaction, which may be anywhere from mildly to severely bothersome (26). Third, ADRs are limited in that they only reflect a small portion of the overall patient experience. Record of the occurrence of ADRs does not instruct in any way how these reactions affect the patient experience. For example, while

physiologic measures may provide important information to clinicians, they are often of limited interest to patients; physiologic measures often correlate poorly with functional capacity and well-being, the areas in which patients are most interested and familiar (27). The severity of an ADR and the overall affect of the medication on well-being are of vital importance in determining whether to continue or stop a medication.

III. Health-Related Quality of Life (HRQOL)

Definition:

Limitations in measuring the occurrence of ADRs in the ambulatory setting and their narrow reflection of the overall patient experience have led investigators to look for better ways to comprehensively estimate the effects of medication use and other physiologic determinants on patients' lives. The QOL outcome measure, as defined previously, is considered to be the most comprehensive and inclusive measure of the patient experience (4); however, from a medical perspective, some of the most important contributors to QOL are health and ability to function. These physical aspects of QOL are encompassed in a more focused health outcome, namely health-related quality of life (HRQOL). HRQOL has become an increasingly important measure in assessing the impact of disease and treatment on individuals.

In public health and in medicine, HRQOL refers to a person's or group's perceived physical and mental health over time (28). It is a multidimensional construct composed of at least four dimensions including physical function, psychological function, social role function, and disease or treatment symptoms (29). HRQOL assessments offer a broad view of health that is consistent with the World Health Organization's

conceptualization of health as a state of physical, mental, and social well-being, not merely the absence of disease and infirmity (30).

HRQOL has been used across multiple disciplines to assess patient function and well-being. For example, physicians have used HRQOL to measure the effects that chronic illness has on a person's day-to-day life. Similarly, public health professionals have used HRQOL to measure the effects of short- and long-term disabilities in different populations (28). HRQOL has also been cited in the cancer literature as a way of describing the effect of both disease and treatment on patient well-being (31).

Findings:

HRQOL has been investigated with respect to age, medical morbidity, and medication use. Similarly to scores of overall QOL, HRQOL scores have also been shown to decline with increasing age. A study by Sato et al. demonstrated that satisfaction with health and physical factors declines in the seventh decade of life, while satisfaction with mental and social factors declines in the eighth decade (32). Similarly to the case with ADRs, the reason behind the association between age and decreased HRQOL is not entirely clear.

A number of studies have examined the association between medication use and HRQOL, but the findings reported in the studies are inconsistent. A study conducted by Henderson et al. suggests that the degree of polypharmacy is inversely related to the physical component of QOL scores (33). While the physical component of QOL scores is not precisely equivalent to HRQOL scores, both measures aim to capture the physiologic determinants of QOL. The reported association between physical QOL scores and medication use remained significant even after controlling for age, sex, and

chronic disease score. Studies by Williams and Fitzpatrick have also reported that the use of multiple prescription medications can have detrimental effects on HRQOL in the elderly (34, 35).

Other studies have reported no significant association between medication use and HRQOL. For example, a recent study of older patients living in rural areas showed that the majority of participants (89 percent) felt that their ability to participate in daily activities was improved by their medications, and only about one-quarter of participants felt that their ability to participate in daily activities was limited by their medications (36). In addition to this qualitative measure, this study also used one-way ANOVAs to compare HRQOL scores among participants who reported using none (0), few (1-2), or multiple (3 or more) prescription medications. There were no significant differences in the physical or mental components of HRQOL scores among study participants in these medication use groups. However, it is important to note that the participants in this study used fewer medications than the national mean for seniors or threshold values used in previous studies (33, 37). Taken together, the findings of these studies suggest that there may be a threshold value for medication use beyond which medication use confers a negative effect on HRQOL.

The literature has also demonstrated a relationship between HRQOL and medical morbidity. A meta-analysis conducted by Fortin et al. considered seven studies, five of which demonstrated an inverse relationship between number of medical morbidities and HRQOL (38). All seven of the studies in the meta-analysis demonstrated that the physical function and symptom components of HRQOL scores were worse in patients with a greater number of medical morbidities; however, two of the studies in the analysis

disagreed with regard to overall HRQOL scores, which also included psychological and social role components. These findings suggest that the decline in HRQOL scores with increasing medical morbidity may be driven by decreases in scores for the physical component of the measure. Another study conducted by Verbrugge et al. further demonstrated an exponential relationship between number of morbidity and HRQOL scores, showing that the presence of multiple chronic conditions negatively influenced health status beyond the sum of the effects of each single condition (39).

Limitations:

In summary, HRQOL has been shown to be directly associated with age and inconsistently associated with medication use; furthermore, the physical component of HRQOL has been shown to be directly associated with number of medical morbidities. However, there are limitations associated with using HRQOL as a health outcome. First, HRQOL can be difficult and cumbersome to measure, because by definition it requires an account of physical, psychological, and social components of the patient experience. Often patient surveys targeted at measuring HRQOL consist of numerous questions and may not be practical to use in a busy clinical setting.

Second, because HRQOL includes so many aspects of patient experience, it has also been criticized by some individuals for being relatively insensitive to specific changes in clinical condition. For example, a randomized study compared patients with low-grade cerebral glioma who received high-dose versus low-dose radiotherapy (40). The results showed that there was no difference in HRQOL scores (based on a 47-question survey), but patients in the high-dose treatment arm reported significantly higher rates of fatigue/malaise and insomnia following treatment. In other words, even though

patients in the high-dose group reported a greater number of and more severe symptoms, this difference was not reflected in their reported HRQOL scores. This lack of association may have occurred because improvements in the psychological or social components of the HRQOL score (eg. due to improved outlook or perspective following the initiation of treatment) balanced any worsening in the symptom component of the HRQOL score. The lack of association may also have occurred because patients were able to recognize treatment-related symptoms as temporary conditions, and thus, they did not significantly impact HRQOL.

The comprehensive nature of HRQOL is both one of its strengths and its difficulties as an outcome measure. Given the difficulty of measuring and estimating HRQOL both on the part of patients and physicians, patient-reported symptom burden has emerged as a more attainable and practical assessment of a patient's health-related experience. Though this measure excludes the psychological and social role components of the HRQOL measure, symptom burden has been shown to be well correlated with HRQOL, and symptom severity has been demonstrated as a strong predictor of HRQOL scores (41). Symptom burden is not a new concept in the literature on disease and treatment, but recent developments in our understanding of how to measure symptoms and their impact make it possible to cast symptom burden as a reasonable summary measure for both disease and treatment outcomes (29).

IV. Symptom Burden

Definition:

Symptoms are inherent to the human experience, and as such, they have been extensively documented since the beginning of the written record. The Ebers and Edwin Smith Papyri from the ancient Egyptian civilization dating back to 2600 BCE provide some of the earliest and most expansive accounts of symptoms, including "excessive urine production" and "rib pain" (29). Today, symptoms continue to be the impetus for nearly half of all ambulatory care office visits (42). Symptoms play a paramount role in a patient's experience of his/her disease.

A *symptom* is defined by Merriam Webster as "something that indicates the presence of bodily disorder; subjective evidence of disease or physical disturbance" (43). "The presence of bodily disorder" has traditionally referred to the presence of disease or acute injury; however, as medicine has evolved and the treatment of disease has become increasingly widespread, symptoms must now be thought of as markers of the presence of the adverse effects of treatment as well (29). "Subjective evidence of disease or physical disturbance" explicates that symptoms are the patient's subjective perception of disease manifestation, and thus, they may only be known through patient report (31). In this way, symptoms differ from signs of disease, such as hypertension and pulmonary edema, which can be objectively measured or observed by the physician.

A symptom can be further conceptualized as multidimensional in nature with components that include frequency, severity, and distress (29). The resultant effect of these dimensions across all symptoms experienced by the patient can be referred to as *symptom burden*. Symptom burden is an entity which encompasses both the severity of

the symptoms and the patient's perception of the impact of all his/her symptoms. Symptom burden is at the heart of the patient experience, and has long been used as a marker of well-being for patients with cancer and other terminal diseases. Symptom burden contributes directly to the physical component of HRQOL and QOL scores.

Findings:

Much of the research on symptom burden has been limited to cancer patients. For example, a number of studies have considered how additional medical morbidities impact symptom burden in cancer survivors. A study conducted by Mao et al. demonstrated an interaction between cancer status and other medical morbidities that resulted in increased symptom burden (44). In this study, cancer survivors with more than three additional medical morbidities reported levels of pain, psychological distress, insomnia, and overall symptom burden three times higher than that of cancer survivors with only one additional medical morbidity. Yancik et al. has also shown the number of medical morbidities to be an independent predictor of morbidity and disability among elderly breast cancer survivors even after controlling for age and cancer stage (45).

In addition to cancer patients, symptom burden has been less extensively explored in patients with chronic medical conditions. Similarly to the treatment of terminal cancer patients, the goal of clinical care for advanced chronic diseases is often to slow disease progression and alleviate disease-associated symptoms (42). In a study surveying community-dwelling older persons with chronic disease, Walke et al. showed that most patients with advanced COPD, cancer, or CHF experienced multiple moderate or severe symptoms; eighty-six percent of participants reported at least one moderate or severe symptom (46). In that study, percentages of patients reporting symptoms such as pain,

dyspnea, anxiety, feelings of depression, and nausea were similar to that reported for hospitalized patients with terminal disease. This finding implies that ambulatory patients with chronic diseases experience levels of symptom burden that are higher than the general population and comparable to hospitalized patients.

Finally, the cancer literature has taken the study of symptom burden one step further, and has applied measures of symptom burden to direct patient management. While many cancer-related symptoms are the result of disease, it has been increasingly recognized that neuropathy, fatigue, sleep disturbance, cognitive dysfunction, and affective symptoms can also be caused by cancer treatment (31). Symptom burden is being used clinically to assess the effect and impact of treatment modalities, including chemotherapy and radiation, in the amelioration of symptoms in palliative care. For example, following a short period of treatment, patients are comprehensively reassessed for new, worsening, or improving symptoms, and changes in overall symptom burden are calculated. Changes in level of symptom burden can then be used to instruct subsequent decisions regarding the continuation or termination of treatment.

Limitations:

While symptoms research has been collected and applied in a clinically useful manner for cancer patients, symptom burden in other patient populations has not been as extensively studied. Furthermore, symptom burden has not been examined as it relates to other factors, such as number of prescribed medications, age, and other socioeconomic markers.

Another limitation of symptom burden as a marker of the overall health experience is that it reflects only a small part of a patient's experience (ie. the physical

component) with illness. Symptom burden scores do not take into account important changes in psychological well-being, future outlook, financial status, and various other factors that may also be affected by the diagnosis of a new medical morbidity or the decision to begin a new treatment (29). These factors may contribute in important ways to a patient's quality of life, and they should also be addressed and optimized. However, these issues may be resolved outside of the decision to start or stop medical treatment, ie. through social/financial consultation and intervention, etc.

Though it is not an all-inclusive measure of HRQOL, symptom burden arguably captures the most important aspect of the patient experience from the perspective of assessing the outcomes of disease and treatment. Because medical treatments and disease processes are most directly manifested as alterations in physiologic systems, these alternations most purely present themselves as changes in symptoms. Consequently, symptom burden is a targeted measure of changes in HRQOL associated with disease and its treatment.

V. Summary of Introduction

In an attempt to improve overall QOL for older patients, it is important first to identify the factors that may be associated with an age-related decline in well-being. While decreasing QOL scores with age may be driven by changes in any of the domains affecting QOL, we have chosen to focus on the role of potential physiologic determinants. As older patients simultaneously suffer a greater number of medical morbidities and receive more health care services, both disease and treatment are two

physiologic determinants which might be associated with the age-related decline in QOL scores discussed earlier.

In the literature to date, both ADRs and HRQOL have been used in various ways to assess changes in patient well-being associated with disease and treatment. However, while both of these measures have been shown to be correlated with age, medication use, and medical morbidity, these measures possess significant limitations in their ability to instruct the clinical management of patients. For example, while ADRs effectively mark the occurrence of medication side-effects, they do not indicate whether or to what extent the patient was disturbed by this reaction. Therefore, if the goal of clinical care is to maximize patient well-being, then following the occurrence of ADRs may not be the most effective way to monitor clinical progress. Likewise, HRQOL has also been used to monitor progress with respect to disease state and treatment. However, because HRQOL theoretically captures multiple aspects of the health-related experience, it can be challenging to discern precisely which aspect is most affecting changes in HRQOL scores. This can make it difficult to identify whether a disease or treatment itself has specifically improved or worsened a patient's physical well-being.

From the perspective of measuring physical well-being, symptom burden is a more practical and targeted measure of the patient experience than HRQOL. For these reasons, we have chosen to use symptom burden to assess the impact of disease and treatment on patient well-being in this study. As previously demonstrated by oncologists, symptom burden can be used as a powerful estimate of the benefit and detriment associated with medical treatment options. To this end, it is a potential tool to be used by

geriatricians, for whom maximizing physical well-being is one of the primary goals of patient care.

Aim of this Study

The overall objective of this study was to determine whether patient well-being, as estimated by self-reported symptom burden, is associated with medical treatment (eg. medication use) and illness (eg. medical morbidities). Specifically, we sought to achieve this aim by independently assessing 1) the association between *medication use* and *symptom burden* and 2) the association between *medical morbidities* and *symptom burden* in older patients. It was hypothesized that symptom burden would increase as the number of prescribed medications increased and as the number of medical morbidities increased.

Methods

I. Participants

Participants in the study were community-dwelling older adults who were enrolled in the primary care clinic of the VA Connecticut Healthcare System, West Haven Campus. Participants were not residents of a nursing home or other extended-care facility during the time of data collection. The inclusion criteria for the study required that participants be aged 65 and older, able to provide consent in English, and without the need of a surrogate for completion of the interview. In total, 166 participants met inclusion criteria. Because only seven of the 166 respondents were female, the decision was made to exclude female patients from the study, as the study was unlikely to have the power to yield statistically significant information regarding gender. The final research cohort included 159 male participants. All participants provided informed consent.

II. Data Collection

The current study is a secondary data analysis of primary data collected between August and December 2007 under the direction of Dr. Joseph Agostini. Original data collection was designed to broadly assess trends in medication use, medical morbidities, and symptom occurrence.

Primary Collection:

Primary data was collected through one-on-one patient interviews conducted in the clinical office setting and through review of electronic medical records. Patients were queried by trained research assistants regarding their age, race, sex, and education level. A Folstein Mini-Mental Status Exam (MMSE) was performed on all patients to assess

mental status; MMSE scores are based on a 30-point scale, where 30 is a perfect score. Information regarding prescribed medications was obtained from the medication list in the VA electronic medical record. Vitamins/supplements were included in the data, but topical ointments were excluded.

Medical morbidities for participants were also assessed through electronic chart review of patient problem lists. Research assistants recorded 19 Charlson comorbidities and three non-Charlson comorbidities for participants in this study, namely hypertension, diabetes mellitus, arthritis, myocardial infarction, peripheral vascular disease, chronic obstructive pulmonary disease (COPD), cancer, congestive heart failure (CHF), depression, stroke, diabetes with organ dysfunction, dementia, peptic ulcer disease, liver disease, renal disease, lymphoma, leukemia, cirrhosis, metastatic malignancy, hemiplegia, tumor (solid), and AIDS.

Symptom occurrence was evaluated through both a patient-directed questionnaire and electronic chart review. Participants were asked if they regularly experienced 18 symptoms, specifically problems with sleep, changes in mood, depression, nausea, diarrhea, constipation, decreased appetite, dizziness, problems with balance, headache, fatigue, confusion, muscular aches, rash, falls, weight loss, difficulty controlling urination, and difficulty thinking. Patients in the study reported the occurrence of 771 symptoms in total at any level of severity. For all symptoms experienced regularly, participants were then asked to rate how bothersome they found the symptom to be on a Likert scale from zero to four, where zero was not bothersome at all and four was severely bothersome. For the purposes of description, we have explicitly assigned a descriptor of severity to each number on the Likert scale as follows, 0 = none, 1 = mild, 2

= moderate, 3 = severe, 4 = very severe. A review of patient charts, including outpatient clinic notes, Emergency Department notes, discharge summaries, and telephone notes, was conducted to assess for any additional symptom documentation by health care providers.

Data Used in Current Project:

For the purposes of data analysis for the current project, the following inclusions and modifications were made to the original data. All medications documented in the primary data set were included in this study. Multiple medications belonging to a single medication class were counted independently (e.g. if a patient was prescribed two forms of insulin, these would be counted as two medications). All recorded medical morbidities were also included in this data analysis.

Classification of symptom data was modified for this study. Some symptoms were excluded and others were combined into symptom groups on the basis of clinical reasoning, literature review, and unclear phrasing of symptoms. Three symptoms were excluded from the analysis because strictly defined they were not symptoms, but rather objective clinical signs; these symptoms included urinary incontinence, falls, and weight loss. Symptoms further excluded from the study due to low rates of patient reporting were rash, headache, and diarrhea; exclusion of these rarely reported symptoms discounted 9.9 percent of total reported symptoms.

Other symptoms were combined into related symptom groups. Decreased mood and depression were combined into a single symptom group because 1) it was unclear clinically that patients would appreciate a difference between these entities and 2) there was a high rate of overlap in positive patient response to these symptoms. Difficulty

thinking and confusion were combined into a single group because it was not clear clinically how these symptoms would be distinguished. Likewise, dizziness and difficulty with balance were combined based on similar clinical reasoning. Finally, nausea and loss of appetite were pooled because these symptoms are clinical corollaries, and there is precedent for combining these entities in the cancer literature (31). The final analysis included eight symptoms/symptom groups, including mood/depression, thinking/confusion, dizziness/balance, nausea/appetite, fatigue, constipation, muscle aches, and problems with sleep.

To obtain a measure of symptom burden for each participant, we created a composite variable indicating the total number of severe or very severe (three or four on the Likert scale) symptoms experienced across the eight symptom groups. Based on clinical judgment, we opted to consider symptoms with a bothersome rating >2 to be clinically significant. This distinction was used because it was thought that patients who were severely or very severely bothered by their symptoms would be willing to modify their medication regimens as a result of their symptoms. Thus, the findings of this study are more likely to mirror true clinical decision making. Each significant symptom added one point to the symptom burden, regardless of whether the symptom was rated as severe or very severe. This measure will provide a conservative estimate for symptom burden.

III. Data Analysis

Data analysis was conducted with SAS version 9.1 (Cary, North Carolina). Baseline characteristics for the study populations were presented with descriptive statistics. To answer the study questions, we used logistic regression analysis to assess

the bivariate association between Symptom Burden and Medication Number and between Symptom Burden and Medical Morbidity Number. We then used multivariate analysis to assess the concurrent associations between Symptom Burden, Medication Number, and Medical Morbidity Number.

IV. Ethical Issues

Written informed consent was obtained from the subjects or their relatives. The study protocol was approved by the VA Connecticut Human Subjects Research Committee.

Results

I. Descriptive Results

Demographic Information:

Table 1 shows the descriptive statistics with reliability estimates for the participants in this study. This study included 159 men who presented to an ambulatory clinic in the VA Connecticut Health Care System. Participants varied in age from 65 to 90 years, and the mean age was 75.7 years. The study population was predominantly Caucasian (90.6 percent), though African American patients (8.2 percent) were also represented at a rate similar to the general population in the state of Connecticut. The frequency of Hispanic patients (1.3 percent) was significantly lower than the frequency in the state of Connecticut population at large (12.0 percent). The mean education level for participants in this study was 11.9 years. The mean result of Folstein Mini-Mental Status Exam for participants was 26.8, which is comparable to MMSE scores reported in other studies of older non-demented adults.

Medical Morbidities:

Table 1 shows the frequency of medical morbidities amongst study participants. Respondents were queried and their medical records were reviewed regarding the presence of 22 medical morbidities. The most commonly reported medical morbidities were hypertension (73.6 percent), diabetes mellitus (39.6 percent), arthritis (30.8 percent), myocardial infarction (19.5 percent), peripheral vascular disease (17.6 percent), cancer (16.4 percent), and COPD (16.4 percent). All other medical morbidities were reported by less than or equal to 10 percent of respondents.

Medications:

The following classes of medications were prescribed to patients in this study: anti-histamines, anti-neoplastic agents, parasympatholytic and sympatholytic drugs, skeletal muscle relaxants, hematologic drugs, cardiac drugs, analgesics and NSAIDs, central nervous system drugs, diuretics, ophthalmic agents, gastrointestinal drugs, endocrinologic drugs, and smooth muscle relaxants.

Table 1. Descriptive Data for Study Participants

	Mean	**SD**	**Range**
Age (yrs)	75.7	6.2	65-90
Education level (yrs)	11.9	2.5	6-19
MMSE	26.8	2.8	18-30
	Frequency	**Percent**	
Male Gender	159	100	
Race			
Caucasian	144	90.6	
African American	13	8.2	
Hispanic	2	1.3	
Medical Morbidity			
Hypertension	117	73.6	
Diabetes Mellitus	63	39.6	
Arthritis	49	30.8	

Table 1 (continued). Descriptive Data for Study Participants

Myocardial Infarction	31	19.5
Peripheral Vascular Disease	28	17.6
COPD	26	16.4
Cancer (all types)	26	16.4
Congestive Heart Failure	17	10.7
Depression	16	10.1
Stroke	14	8.8
DM with organ dysfunction	6	3.8
Dementia	5	3.1
Peptic Ulcer Disease	4	2.5
Liver Disease	1	0.6
Renal Disease	1	0.6
Lymphoma	1	0.6
Cirrhosis	1	0.6
Cancer (metastatic)	1	0.6
Hemiplegia	0	0.0
Tumor (solid)	0	0.0
Leukemia	0	0.0
AIDS	0	0.0

Symptoms:

Study participants were asked about the regular occurrence and severity of eight symptoms/symptom groups. At any level of severity (0-4), patients reported a total of 504 symptoms across all symptom groups, and all but one symptom (nausea/decreased

appetite) was reported by at least one-third of participants. The symptom groups that were most commonly reported by respondents were dizziness/balance (56.6 percent of respondents), depressed mood/depression (47.2 percent), and fatigue (42.8 percent). Difficulty sleeping and muscles aches were also reported by 41.5 percent of respondents. Table 2 shows the frequency of symptom reporting at any severity by respondents.

Symptom prevalence was also assessed for symptoms only at severe and very severe levels. When only these more severe symptoms were included, patients reported a total of 119 symptoms. At least one severe or very severe symptom was reported by fifty-three (33.3 percent) respondents. The most commonly reported symptoms were dizziness/problems with balance (15.7 percent), muscle aches (11.9 percent), and difficulty sleeping (11.3 percent). All other symptoms were reported by less than or equal to 10 percent of respondents. Frequencies of symptom reporting are displayed in Table 2.

Table 2. Frequency of Symptoms at Any Severity Level and at Severe/Very Severe Levels

	Any Severity Level		Severe/Very Severe	
Symptom Group	**Frequency**	**Percent**	**Frequency**	**Percent**
Dizziness/Balance	90	56.6	25	15.7
Mood/Depression	75	47.2	16	10.1
Fatigue	68	42.8	11	6.9
Difficulty Sleeping	66	41.5	18	11.3
Muscle Aches	66	41.5	19	11.9
Thinking/Confusion	51	32.1	16	10.1
Constipation	51	32.1	6	3.8
Nausea/Decreased Appetite	37	23.3	8	5.0

The results of this study further show that dizziness/balance was the most commonly reported symptom when all severity levels were considered and when only severe/very severe levels were considered. Mood/depression and fatigue were commonly reported at any severity level, but these symptoms were relatively less commonly reported at severe/very severe levels. In contrast, difficulty with thinking/confusion was a less prevalent symptom when all severity levels were considered, but a relatively higher percentage of patients who reported this symptom rated it as severe/very severe. These results are displayed in Table 3.

Table 3. Percent of Symptomatic Participants Reporting Their Symptom as Severe or Very Severe

Symptom Group	Any Severity Level	Severe/Very Severe	Percent Reporting Severe/Very Severe
	Number	Number	Percent
Dizziness/Balance	90	25	27.8
Mood/Depression	75	16	21.3
Fatigue	68	11	16.2
Sleep	66	18	27.3
Muscle aches	66	19	28.8
Thinking/Confusion	51	16	31.4
Constipation	51	6	11.8
Nausea/Decreased Appetite	37	8	21.6
Total	504	119	23.6

Symptom Burden:

Based on the results of symptom reporting, symptom burden (including only severe and very severe symptoms) was calculated for each patient. Symptom burden for participants ranged from zero to five. Results showed that the mean symptom burden was 0.63 +/- 1.06, and 66.7 percent of respondents reported a symptom burden of zero. Though the patients with a symptom burden equal to zero did not report any severe or severe symptoms, they still may have reported any number of mild or moderate symptoms. Table 4 shows the number of patients reporting a given level of symptom burden.

Table 4. Frequency of Patients Reporting a Given Level of Symptom Burden

Symptom Burden	Frequency	Percent
0	106	66.7
1	24	15.1
2	15	9.4
3	11	6.9
4	2	1.3
5	1	0.6
Mean, SD	0.63, 1.06	
Median	0	

II. Inferential Results

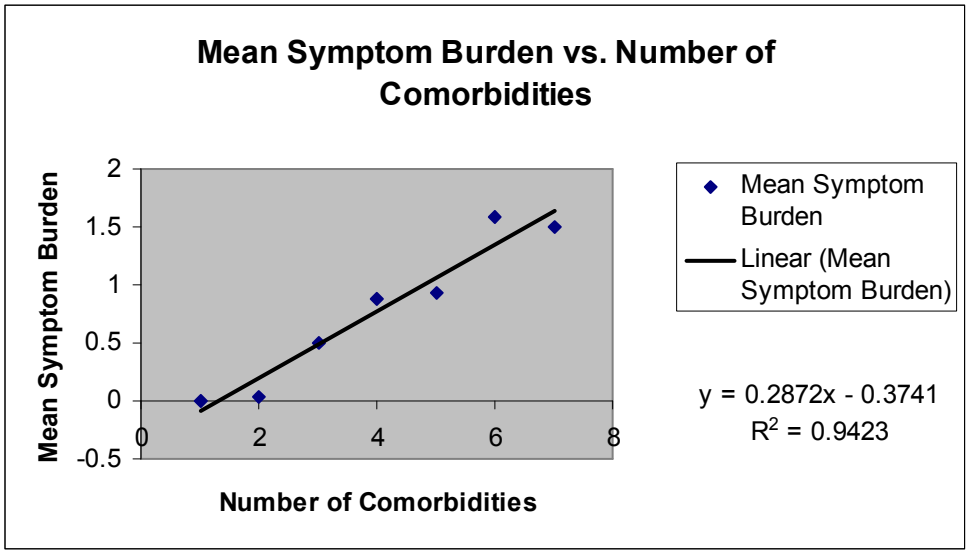
The first objective of this study was to identify and characterize any association between number of Medical Morbidities and Symptom Burden. The total number of medical morbidities experienced by patients in the study varied from zero to six. The mean number of medical morbidities per patient was 2.56 +/- 1.36. To simplify our data analysis, we calculated the mean symptom burden for all participants reporting each number of medical morbidities. We then charted the mean symptom burden versus the number of medical morbidities. Table 5 demonstrates the number of respondents that reported a given number of medical morbidities and the mean symptom burden per number of medical morbidities.

Table 5. Frequency and Mean Symptom Burden of Patients Reporting a Given Number of Medical Morbidities

Number of Medical Morbidities	Frequency	Percent	Mean Symptom Burden	SD
0	4	2.5	0.00	0.00
1	38	23.9	0.03	0.16
2	40	25.2	0.50	1.04
3	35	22.0	0.89	1.13
4	28	17.6	0.93	1.05
5	12	7.6	1.58	1.56
6	2	1.3	1.50	0.71
Mean, SD	2.56, 1.36			
Median	2			

The association between mean symptom burden and number of medical morbidities was examined through bivariate linear regression analysis. As the number of medical morbidities increased from zero to six, symptom burden increased on average by 0.29 for each additional morbidity ($R^2 = 0.9423$). Figure 1 graphically depicts the association between mean symptom burden and number of medical morbidities.

Figure 1. Mean Symptom Burden vs. Number of Medical Morbidities



The second objective of this study was to identify and characterize any association between Number of Medications and Symptom Burden. The number of medications prescribed for patients in this study varied from one to 18. The mean number of medications was 7.91+/- 2.83. All patients in the study took at least one medication. In this study, 96.9 percent of patients took five or more medications, and 27.7 percent of patients took 10 or more medications. These figures are somewhat higher than those reported in previous studies for patients over 65. For each number of prescribed medications, mean symptom burden was calculated for all patients taking this number of medications. Table 6 shows the frequency of patients prescribed a given number of medications and the mean symptom burden for patients prescribed each number of medications.

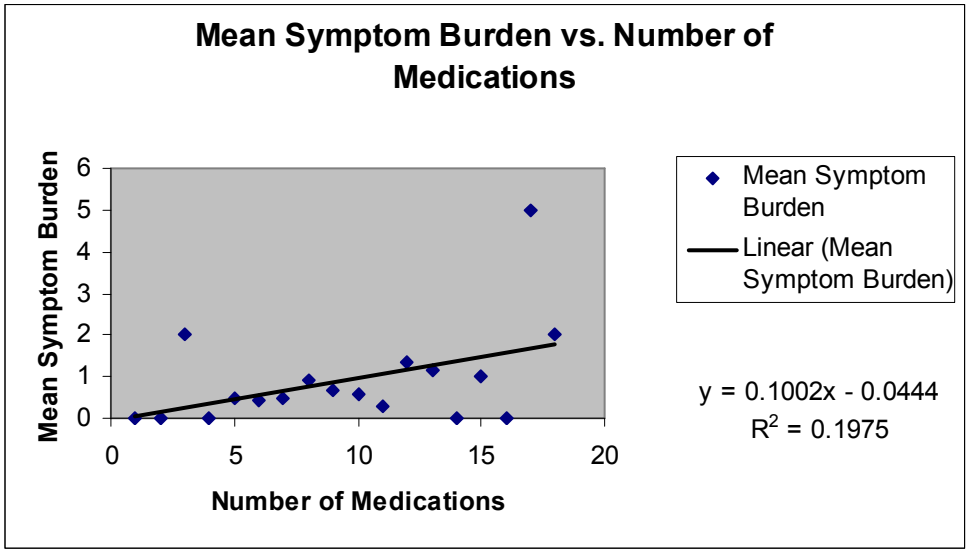
Table 6. Frequency and Mean Symptom Burden of Patients Prescribed a Given Number of Medications

Number of Medications	Frequency	Percent	Mean Symptom Burden	SD
1	1	0.6	0.00	.
3	1	0.6	0.00	0.00
4	3	1.9	2.00	.
5	35	22.0	0.00	0.00
6	18	11.3	0.46	0.74
7	24	15.1	0.44	0.86
8	14	8.8	0.50	1.02
9	20	12.6	0.93	1.49
10	16	10.1	0.65	1.14
11	10	6.3	0.56	0.96
12	6	3.8	0.30	0.95
13	6	3.8	1.33	1.03
14	1	0.6	1.17	1.17
15	2	1.3	0.00	.
17	1	0.6	1.00	0.00
18	1	0.6	0.00	0.00
Mean, SD	7.91, 2.83			
Median	7			

The association between mean symptom burden and number of medications was examined through bivariate linear regression analysis. As the number of prescribed

medications increased from one to 18, symptom burden increased by 0.1 for each increase in number of medications ($R^2 = 0.1975$). Figure 2 graphically demonstrates the association between number of medications and mean symptom burden.

Figure 2. Mean Symptom Burden vs. Number of Prescribed Medications



To estimate the independent effect that medication use and medical morbidities has on symptom burden, a multivariate regression analysis was conducted. When the number of medical morbidities was controlled for as a confounder, the association between number of prescribed medications and symptom burden was reduced from 0.1 to 0.04 ($p = 0.17$).

Discussion

The results of our study demonstrate a positive correlation between medical morbidity and symptom burden, but no correlation between medication use and symptom burden.

I. Medical Morbidity and Symptom Burden

In our study, as the number of medical morbidities increased from zero to six, symptom burden increased by an average of 0.29 points with the addition of each subsequent medical morbidity. The correlation between these two variables was best modeled using a linear regression ($R^2 = 0.94$), and this association held true after we controlled for patient age and number of prescribed medications.

The demonstrated correlation between medical morbidity and symptom burden is a clinically reasonable one. As medical morbidities are most often associated with the occurrence of symptoms, it is logical that an increase in the number of medical morbidities would result in an increase in the level of symptom burden. Additionally, patients who suffer from a greater number of medical morbidities are more likely to visit a higher number of medical specialists (12); it is conceivable that this increased interaction with health care providers offers these patients more opportunity to report symptoms, which would then be documented in the medical record and reflected in our symptom burden calculations.

Though a direct correlation between medical morbidity and symptom burden seems clinically reasonable, there have been no studies in the literature to date explicitly examining this relationship in older patients. However, our reported association is

consistent with much of what has previously been reported on the correlation between medical morbidity and other QOL measures. For example, a meta-analysis conducted by Fortin et al. considered seven studies, five of which demonstrated an inverse relationship between number of medical morbidities and HRQOL (38). Though the studies in Fortin's meta-analysis focused on HRQOL as an outcome, symptom burden has been shown in previous studies to be an important contributor to HRQOL scores and has been shown to correlate strongly with these scores (41).

Of the studies included in Fortin's meta-analysis, all seven demonstrated diminished values for the physical component of HRQOL scores in patients with a greater number of medical morbidities; however, some of the studies in the meta-analysis disagreed regarding the association between *overall* HRQOL scores and number of medical morbidities (47). Our study focused only on data (ie. symptom burden) that most strongly impact the physical component of HRQOL. The direct correlation that we found between number of medical morbidities and symptom burden supports the works compiled by Fortin et al. and suggests that it is the *physical* component of illness that drives the decline in HRQOL associated with increasing medical morbidity. This implies that the spiritual, intellectual, and social components of QOL measures may have a weaker correlation with medical morbidity.

Previous studies have reported the conditions which most negatively impact QOL to be rheumatoid arthritis and back problems (48). These reports are consistent with our finding that muscles aches is one of the symptoms most commonly reported as severe or very severe. It is possible that compared with other medical morbidities, the relationship

of each of these medical conditions with pain causes these conditions to be more bothersome to patients.

Our findings on medical morbidity and symptom burden also differ from some previously reported studies. For example, a study by Cassileth demonstrated that HRQOL scores for five groups of physically ill patients (suffering from arthritis, diabetes, cancer, renal disease, or dermatologic disorders) did not differ significantly from those of the general public (49). However, unlike our study, Cassileth's investigation only compared patients with a single chronic condition to persons in the general public with no known chronic conditions. Cassileth's study did not examine the cumulative contribution of number of medical morbidities. Combined with the conclusions drawn by Cassileth, the findings of our study suggest that there may be a dose-dependent relationship between medical morbidity and symptom burden. Thus, it is quite possible that the occurrence of a single medical morbidity has only a minimal effect on symptom burden; but, as the number of medical morbidities increases, their cumulative effect on symptom burden becomes significant.

Finally, a previous study conducted by Verbrugge showed that the level of disability incurred by patients increased exponentially with the accumulation of additional medical morbidities (39). In other words, the presence of multiple chronic conditions increased the burden of disease and negatively influenced health status beyond the sum of the effects of each single condition. While the results of our study do not duplicate this exponential association between medical morbidity and symptom burden, our results do demonstrate a linear correlation between these two variables.

In summary, the results of our study expand the work that others have done regarding the impact of medical morbidity on various measures of patient well-being. While QOL and HRQOL have been linked to medical morbidities in the past, our study further suggests that this linkage may be driven by changes in symptom burden, which would be reflected in the physical component of QOL and HRQOL scores. Our study also suggests that the association between medical morbidity and symptom burden is linearly dose-related.

II. Medication Use and Symptom Burden

The results of our study do not demonstrate a statistically significant association between medication use and symptom burden in older patients. As the number of prescribed medications increased from one to 18, symptom burden increased by an average of 0.1 points for each additional medication ($R^2 = 0.1975$). However, after the number of medical morbidities was controlled for as a confounding factor in the analysis, symptom burden increased by an average of only 0.04 points for each additional medication.

Our findings differ from those reported by previous studies in the literature, many of which do show an association between medication use and various measures of patient well-being. While there have been no studies to date which specifically explore the relationship between medication use and symptom burden, a number of studies have investigated the association between medication use and ADRs (33, 35, 50). While it may be true that patients taking more medications suffer a greater number of ADRs, our study suggests that the occurrence of these adverse reactions does not significantly

impact symptom burden. For instance, many patients may not be aware that they are experiencing ADRs, or they may only be minimally bothered by these reactions.

There have also been studies reported in the literature that directly consider the association between medication use and QOL scores; however, the results of these studies are conflicting. A study conducted by Henderson suggests that the degree of medication use is inversely related to the physical component of QOL scores (33). Although this study did control for six medical morbidities, it did not control for some important morbidities, including cardiovascular disease and renal disease. The study was also limited to a population of American Indians. In contrast, the results of a study conducted by Graffen demonstrated that in a rural elderly population, there was no demonstrated association between medication use and lower QOL scores (37).

Our study does not investigate the reasoning behind the reported lack of association between medication use and symptom burden. However, based on clinical reasoning, we conjecture that perhaps the benefits and detriments associated with medication use counterbalance one another. It is possible that any benefit in symptom relief conferred by the addition of a new medication is offset by any adverse effects also associated with the use of this new medication, including the occurrence of ADRs. For example, adding a beta blocker to a medication regimen may improve symptoms of angina and palpitations, but it may concurrently cause dizziness and fatigue, resulting in no net change in overall symptom burden.

III. Limitations and Strengths of the Study

Our investigation has several limitations. First, the cross-sectional design of our study precludes the determination of causality of the associations we observed. While we have shown that medical morbidities and symptom burden are associated with one another, it cannot be determined whether this increase in symptom burden results directly from the presence of these disease states. However, it is reasonable from a clinical perspective to assume that medical conditions do result in the development of symptoms and impact symptom burden.

A second potential limitation of this study is recall bias. The symptoms reported by patients in this study were not necessarily present at the time of the interview. It is conceivable that individuals might have experienced other symptoms that they did not report, or conversely, that they may have forgotten to report symptoms that they did experience. However, since we only included severe and very severe symptoms in our symptom burden calculations, it is more likely that participants' recall of symptoms was accurate, as a person may be more likely to remember a more severe symptom. One might also expect that severe or frequent symptoms would be more likely to be reported by patients to physicians and thus be recorded in the medical record.

A final set of limitations of this study stems from the characteristics of our sample population. Because our study was restricted to community-dwelling older male patients, we cannot generalize our results to women, non-community dwelling patients, or younger patients. Conflicting studies have reported both male and female gender as potential risk factors for ADRs; this study does not clarify that association. We also do not report on the effects that other potential confounding variables may have on symptom

burden, including socio-demographic status, health habits, and social support, all of which have been recognized as impacting QOL in older persons (51). Furthermore, we cannot be certain that our questionnaire includes all of the symptoms important to community-dwelling patients; at present, there is no generally accepted list of the most important symptoms for this population. Finally, it is possible that this study was underpowered to detect an association between medication use and symptom burden.

IV. Study Implications

It has been previously demonstrated that older patients suffer from a greater number of medical morbidities and receive more medical services than their younger counterparts. Though many experts believe that the provision of abundant health care for older individuals has resulted in extended life expectancy, the literature continues to show that older patients report an age-related decline in QOL (3). This trend highlights the management of symptom burden as an area of potential improvement in the care of older patients. As was discussed earlier in this paper, it is not clear from the existing literature whether this decline in QOL may arise in association with increased medical morbidity, increased medical treatment, or both.

The first major implication drawn from this study is based on our reported positive association between medical morbidity and symptom burden. This finding implies that the previously reported decline in QOL associated with increasing number of medical morbidities may be at least partly driven by an increase in symptom burden. Increased symptom burden directly impacts the physical component of QOL and HRQOL scores. This conclusion suggests that mitigating symptom burden should be a

targeted outcome for patients who designate improved QOL as one of their primary goals of medical care.

In an effort to alleviate symptom burden, there are many strategies which can be employed by both physicians and patients. Some potential strategies include physical therapy, massage therapy, pharmacotherapy, lifestyle modifications, and alternative medicine therapies. Given the low adverse effect profile of most of these interventions, physicians may consider counseling their patients regarding these strategies in an attempt to reduce physical symptoms and improve QOL. The results of our study suggest that the management of symptoms is a goal of care which should be considered as important as extending life and preventing illness.

The second implication drawn from this study is based on the lack of association we reported between medication use and symptom burden. To improve symptom burden, our findings imply that we may gain the most benefit from reducing medical morbidity, irrespective of the number of medications that patients are prescribed. However, a number of reputable studies have demonstrated that a high level of polypharmacy is a risk factor for falls and the occurrence of other ADRs in older patients (17, 52). In light of these findings, we do support limiting the use of multiple medications as much as possible.

If our goal in prescribing medications to this population is to reduce symptom burden while still limiting polypharmacy, then one strategy for achieving these outcomes may be to focus on the prescription of medications intended to reduce symptom burden, as opposed to medications that are intended to prevent disease development/progression. Many medications are prescribed to extend life and prevent the development of disease,

but these medications may not confer major improvements in symptom reduction. This may be true for some of the most commonly prescribed medications for older patients, including ace-inhibitors and diuretics for hypertension, anti-depressants for mild mood disorders, aspirin and warfarin for anti-coagulation, and statins for hypercholesterolemia. Though these medications bestow a benefit in long-term health outcomes and life expectancy, they often do not contribute to perceptible changes in symptom burden. In contrast to those prevention-centered medications, some medications are targeted specifically at improving symptoms. In terms of reducing symptom burden, it is important to continue these medications which directly improve symptoms associated with medical morbidities. Analgesics are an example of an important symptom-centered medication.

In addition to talking with patients regarding real-time changes in symptom burden and various strategies to improve symptom burden, this study also highlights the importance of talking with patients extensively about their goals of medical care. In managing the care of older patients with multiple medical conditions, patients should be advised that there may be trade-offs to consider regarding improvements in life expectancy and quality of life. As discussed above, some medical treatments and lifestyle modifications might advance one of these objectives more than the other, or even at the expense of the other. Patients' priorities on these issues will vary from person to person, and they may instruct physicians as to whether or not to continue a particular medication. This technique has been used effectively by oncologists in patients with terminal disease (29).

V. Future Research

Additional studies that longitudinally examine the associations reported in this study would add to the existing body of knowledge. While a number of longitudinal studies following the natural course of aging have been conducted, these studies have not explicitly investigated the association between medical treatment, medical morbidity, and overall symptom burden. In a potential longitudinal study, a cohort of older patients could be followed throughout the natural course of aging. Patients could be followed as new disease processes develop, progress, and are treated with various medical treatments. Throughout this time period, symptom burden could be repeatedly measured by health care providers at specified time intervals, and symptom burden, medication use, and medical morbidity burden could then be correlated over time.

Future research could also be pursued within the confines of a cross-sectional analysis. Building on the association we reported between medical morbidities and symptom burden, a future study might consider whether particular medications or medication classes drive trends in symptom burden. For example, the addition of a beta-blocker to a medication regimen may reduce symptom burden more or less than the addition of a daily aspirin. Future research might also be done to determine which symptoms are associated with the greatest increase in symptom burden; these findings would help direct the targets for pharmacotherapy.

Finally, to further support the conclusions and recommendations drawn from this study, it should be determined whether symptom-directed changes in medication regimens lead to a reduction in symptom burden and HRQOL over time. This conclusion could be investigated by querying patients regarding symptom occurrence and severity

following medication changes and comparing the strength of the association between symptom burden and medication use in this population to that of a control group in whom symptoms were not explicitly discussed.

Conclusion

Much time and resources have been spent in the pursuit of the ideals expressed by Dr. William Mayo to improve both quantity and quality of human life. While advances in medicine have allowed us to make great strides in prolonging life, in regards to furthering the quality of life in older patients, the research suggests that there remains room for improvement. An understanding of the barriers and facilitators that affect HRQOL throughout the life course is important for identifying those at risk for less than optimal quality of life and for designing appropriate health-promoting interventions.

This study investigated the effect that medical morbidity and medication use have on one physiologic determinant of HRQOL, namely, symptom burden. Of the two determinants considered, the presence of medical morbidity was shown to have a stronger negative effect on symptom burden than was medication use. These findings suggest that physicians should focus more attention on the alleviation of symptoms associated with medical morbidities in an attempt to improve QOL for their patients. There are many strategies which can be employed by both physicians and patients to reduce symptom burden, and physicians should encourage their patients to trial these strategies in an attempt to improve physical symptoms and QOL.

In conclusion, this study has employed a patient-centered health outcome to measure the impact that both disease and treatment have on quality of life. As we continue to strive to slow the decline in HRQOL experienced by older patients, further research should be done to identify and assess other factors which may also contribute to this decline. Only through sustained inquiry can we identify methods through which

society can foster an individual's HRQOL, particularly as that person faces the possibility of frailty and dependence associated with age.

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