Prevalence, Expenditures, and Complications of Multiple Chronic Conditions in the Elderly

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Background: The prevalence, health care expenditures, and hospitalization experiences are important considerations among elderly populations with multiple chronic conditions.

Methods: A cross-sectional analysis was conducted on a nationally random sample of 1217,103 Medicare fee-for-service beneficiaries aged 65 and older living in the United States and enrolled in both Medicare Part A and Medicare Part B during 1999. Multiple logistic regression was used to analyze the influence of age, sex, and number of types of chronic conditions on the risk of incurring inpatient hospitalizations for ambulatory care sensitive conditions and hospitalizations with preventable complications among aged Medicare beneficiaries.

Results: In 1999, 82% of aged Medicare beneficiaries had 1 or more chronic conditions, and 65% had multiple chronic conditions. Inpatient admissions for ambulatory care sensitive conditions and hospitalizations with preventable complications increased with the number of chronic conditions. For example, Medicare beneficiaries with 4 or more chronic conditions were 99 times more likely than a beneficiary without any chronic conditions to have an admission for an ambulatory care sensitive condition (95% confidence interval, 86-113). Per capita Medicare expenditures increased with the number of types of chronic conditions from $211 among beneficiaries without a chronic condition to $13,973 among beneficiaries with 4 or more types of chronic conditions.

Conclusions: The risk of an avoidable inpatient admission or a preventable complication in an inpatient setting increases dramatically with the number of chronic conditions. Better primary care, especially coordination of care, could reduce avoidable hospitalization rates, especially for individuals with multiple chronic conditions.

Arch Intern Med. 2002;162:2269-2276

Previous studies have shown that as much as 45% of the general population and 88% of the population aged 65 years and older have 1 chronic condition or more and that more than 75% percent of all US health care expenditures are related to the treatment of chronic conditions. The prevalence of chronic conditions continues to increase, and by 2020 an estimated 157 million Americans (nearly 50% of the population) are projected to have at least 1 chronic condition. Therefore, it is not surprising that considerable attention has been directed toward designing treatment protocols to prevent or inhibit the progression of specific chronic conditions such as diabetes, asthma, or stroke. Sophisticated pharmacological therapies, disease management programs, and patient education efforts have been developed in an attempt to prevent progression of specific chronic conditions and to improve ongoing disease management. However, with rare exceptions, nearly all of these initiatives have focused on a single chronic condition. Relatively few initiatives address the reality that 50% of all individuals with chronic conditions have multiple chronic conditions. In 2000, an estimated 57 million Americans had multiple chronic conditions, and the number is projected to increase to 81 million by 2020.

Individuals with multiple chronic conditions have clinical needs that may differentiate them from persons with a single chronic condition. Evidence indicates that chronic conditions cluster, and that persons with 1 chronic condition are more likely to have other conditions. Moreover, persons with multiple chronic con-
conditions may have more rapid declines in health status and a greater likelihood of disability. In terms of medical treatment, poor coordination of clinical services may predispose persons with multiple chronic conditions to errors of both omission and commission, such as adverse drug-drug interactions. One study found that individuals with chronic conditions were less likely to receive important routine outpatient medical treatments that were unrelated to their chronic condition. Contraindicated medical care may be especially problematic among the elderly population, as seniors are at greater risk for having multiple chronic conditions and may be more susceptible to complications of treatment as a result of physical frailty, complicated drug regimens, and poor coordination of care.

Our goal was to enhance understanding of the prevalence, expenditures, rate of hospitalizations for ambulatory care sensitive conditions (ACSCs), and frequency of preventable complications associated with hospitalization among Medicare beneficiaries with multiple types of chronic conditions. Inpatient hospitalizations for ACSCs have been defined as conditions for which timely and effective primary care may help to reduce the risks of hospitalization by preventing the onset of a condition, controlling an acute episodic illness, or managing a chronic condition. Preventable complications that are incurred during hospitalization indicate adverse events that arise during the course of treatment as a result of complications of surgery or iatrogenic events. We identify the most prevalent types of chronic conditions and the most commonly occurring combinations of chronic conditions, as well as direct medical expenditures by the Medicare program for aged Medicare beneficiaries with specific combinations of chronic conditions. We hypothesize that individuals with more types of chronic conditions would be increasingly likely to incur inpatient admissions for ACSCs and to incur preventable complications during hospitalization.

STUDY DESIGN AND POPULATION

This study, which was a nationally representative, cross-sectional study of the treated prevalence of chronic conditions among aged Medicare beneficiaries in 1999, included individuals aged 65 years or older, living in the United States, and enrolled in the Medicare program with both Part A and Part B fee-for-service coverage during the calendar year 1999. Individuals who died during calendar year 1999 were also included in this study. As encounter and expenditure data for beneficiaries enrolled in managed care plans were not available, participants in Medicare managed care were excluded from this analysis.

Data were obtained from a 5% nationally representative random sample of paid claims for Medicare beneficiaries in the calendar year 1999. The file, maintained by the Centers for Medicare & Medicaid Services (formerly the Health Care Financing Administration), Baltimore, Md, is commonly used for research purposes. The enrollment file contains demographic information on each Medicare beneficiary, and the claims files contain expenditure and utilization data at the individual beneficiary level for all services covered by Medicare. We combined the enrollment and claims files to develop individual records for each Medicare beneficiary in our sample. Our data set contains information on all inpatient hospital, skilled nursing facility, home health care, outpatient hospital, and Part B (physician) encounters incurred by eligible beneficiaries during 1999. Expenditures are the amount paid by the Medicare program. Expenditure information was not available on deductibles and coinsurance paid by Medicare beneficiaries and does not include services such as prescription drugs that may have been used by beneficiaries but that were not covered by Medicare.

DEFINITION OF CHRONIC CONDITIONS

Medicare beneficiaries with chronic conditions were identified using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)1 diagnosis codes assigned by health care providers to administrative claims. Ambulatory diagnostic groups (ADGs) from the ambulatory care group (ACG) classification system were used to identify ICD-9-CM diagnoses associated with chronic conditions. The ACG system is a case-mix methodology that relies on ambulatory and inpatient administrative claims data. Details of the ACG system have been previously published. The ADG clusters are the building blocks of the ACG system and are used to assign each ICD-9-CM diagnosis into 1 of 32 unique diagnostic morbidity clusters based on a variety of factors, including clinical similarity, likelihood of persistence or recurrence, and expected need for continued treatment. The ADG clusters take into account many of the factors that are used to define chronic conditions and therefore were used to identify specific chronic condition diagnosis codes.

We identified 12 of 32 ADG clusters (representing a total of 3493 five-digit ICD-9-CM codes) that involve chronic conditions (ie, asthma, stable and unstable chronic medical conditions, stable and unstable chronic specialty conditions, psychosocial conditions, and malignancy). To be classified as having a chronic condition, Medicare beneficiaries must have incurred at least 1 inpatient, skilled nursing facility, or home health care medical claim or 2 or more outpatient hospital or Part B medical claims with 1 or more ICD-9-CM diagnosis codes that met our definition for chronic illness. All codes, not just primary diagnostic codes, were reviewed. The requirement of 2 or more outpatient or Part B medical claims for each diagnosis was to minimize rule-out diagnoses.

We grouped the individual ICD-9-CM codes by main organ system involvement (major diagnostic category, or MDC). There are a total of 24 MDCs that represent a broad classification of diagnoses typically grouped by organ system (MDC 23, “Other Factors,” was excluded as it is a loose amalgamation of unrelated conditions). While each MDC may include a large number of chronic conditions that may be defined as comorbidities, we selected MDCs as the unit of comorbidity analysis because conditions within each MDC are likely to be treated by a single type of physician specialty. Individuals with conditions in more than 1 MDC are likely to be treated by more than 1 type of specialist and might therefore be at greater risk for breakdowns in coordination of medical care. For example, an individual diagnosed with hypertension, heart failure, and hypercholesterolemia would be characterized as having 2 types of chronic conditions, as hypertension and heart failure both fall within MDC 5, “Diseases and Disorders of the Circulatory System,” and hypercholesterolemia falls into MDC 10, “Endocrine, Nutritional, and Metabolic Diseases and Disorders.” An individual with diabetes (MDC 10, “Endocrine, Nutritional, and Metabolic Diseases and Disorders”), renal fail-
ture (MDC 11, “Diseases and Disorders of the Kidney and Urinary Tract”), and diabetic retinopathy (MDC 2, “Diseases and Disorders of the Eye”) would be characterized as having 3 types of chronic conditions. Such a classification of conditions partially addresses the issue of severity, as multiple system involvement generally suggests greater severity than single system involvement.

CLINICAL OUTCOMES

To identify ACSCs in the Medicare population, we examined primary and supplemental diagnoses listed on inpatient hospitalization administrative claims that originally were identified as ACSCs. More recent studies have evaluated ACSC clarity and partially addresses the issue of severity, as multiple system types of chronic conditions. Such a classification of conditions on the risk of incurring clinical outcomes of interest. The natural logarithm of the logistic regression coefficient provides estimates of the odds ratio of incurring a hospitalization for ACSCs and the odds ratio of incurring a preventable complication during hospitalization. Data management and statistical analyses were performed using a commercially available statistical software package.

PREVALENCE AND EXPENDITURES

As shown in Table 2, 82% of aged Medicare beneficiaries had 1 or more types of chronic conditions. The prevalence of chronic conditions increased with age from 74% of those aged 65 to 69 years to 88% of Medicare beneficiaries aged 85 years and older. Within each age stratum, women were slightly more likely (1%-4%) than men to have chronic illness. A total of 65% of participants were found to have 2 or more types of chronic conditions, 43% of participants had 3 or more types of chronic conditions, and 24% had 4 or more types of chronic conditions. The probability of having multiple types of chronic conditions increased with age. On average, study participants had 2.34 types of chronic conditions, increasing by age from 1.88 types of chronic conditions per beneficiary aged 65 to 69 years to 2.71 types of chronic conditions among individuals aged 85 years and older.

Medicare expenditures were concentrated among beneficiaries with multiple types of chronic conditions. Mean per capita Medicare expenditures during 1999 were $5015. Per capita Medicare expenditures increased with number of types of chronic conditions, rising from $211 among individuals without any chronic conditions to $1154 for individuals with 1 type of chronic condition, $2394 for individuals with 2 types of chronic conditions, $4701 for individuals with 3 types of chronic conditions, and $13973 among individuals with 4 or more types of chronic conditions. Individuals without any chronic conditions accounted for 18% of all study participants, but just 1% of all Medicare beneficiaries. Individuals with 2 or more types of chronic conditions represented 65% of Medicare beneficiaries, but 95% of Medicare expenditures.

Chronic condition prevalence, Medicare expenditures, and comorbidity varied widely among the 16 most common MDCs, as shown in Table 3. The 8 remaining MDCs captured fewer than 1% of all Medicare beneficiaries. More than half of all study participants were found to have a chronic condition related to diseases and disorders of the circulatory system (38%), followed by endocrine, nutritional, and metabolic diseases and disorders of the eye (10%), and respiratory system (7%). Mean per capita Medicare expenditures during 1999 were $2394 for individuals with 2 types of chronic conditions.
ders (43%). While the level of comorbidity was high across all MDCs, there was considerable variability by MDC in the percentage of individuals who had multiple types of chronic conditions. For example, 80% of all individuals with chronic conditions related to MDC 17, “Myeloproliferative Diseases and Disorders and Poorly Differentiated Neoplasm,” were found to have 4 or more other types of chronic conditions, in comparison with 38% of individuals with chronic conditions related to MDC 5, “Diseases and Disorders of the Circulatory System.” While there was substantial variation in per capita Medicare expenditures among MDCs, much of this variation may be attributable to the percentage of individuals with comorbidity.

CLINICAL OUTCOMES

There were a total of 459,658 inpatient admissions incurred by study participants during 1999. Approximately 10% of these hospitalizations were for ACSCs. There were 49,593 hospitalizations for ACSCs, representing a rate of 40.7 hospitalizations for ACSCs per 1000 Medicare beneficiaries. Approximately 90% of admissions for ACSCs were related to 4 conditions: bronchopneumonia (48%), volume depletion (16%), ischemic heart disease and hypertension (19%), and cerebrovascular disease and hypertension (7%). Rates of hospitalization for ACSCs increased with age, rising from 21.3 per 1000 beneficiaries between 65 and 69 years of age to 82.1 per 1000 beneficiaries aged 85 years and older.

A total of 23,551 hospitalizations with preventable complications were incurred among study participants during 1999, representing 19.4 hospitalizations with preventable complications per 1000 study participants. Approximately 60% of hospitalizations with preventable complications were related to 5 conditions: hemorrhage or hematoma complicating a procedure (17%), postoperative infection (13%), cardiac complications (12%), gastrointestinal complications (10%), and respira-
atory complications (8%). Rates of hospitalization with preventable complications were not strongly associated with age, ranging from 16.2 per 1000 beneficiaries among individuals aged 65 to 69 years to 22.3 complications per 1000 beneficiaries aged 80 to 85 years. Individuals within the oldest age group (≥85 years) incurred an average of 16.8 hospitalizations with preventable complications per 1000 beneficiaries, a rate similar to that observed for Medicare beneficiaries aged 65 to 69 years.

Rates of both inpatient admissions for ACSCs and with preventable complications increased dramatically with greater numbers of types of chronic conditions. As shown in the Figure, inpatient admissions for ACSCs increased incrementally from 1.0 per 1000 beneficiaries without any chronic condition to 7.7 per 1000 beneficiaries with only 1 type of chronic condition, 19.5 per 1000 beneficiaries with 2 types of chronic conditions, 40.2 per 1000 beneficiaries with 3 types of chronic conditions, and 362.5 per 1000 beneficiaries with 10 or more types of chronic conditions. Likewise, hospitalizations with preventable complications increased from 0.6 per 1000 beneficiaries without a chronic condition to 3.6 per 1000 beneficiaries with only 1 type of chronic condition, 8.1 per 1000 beneficiaries with 2 types of chronic conditions, 17.4 per 1000 beneficiaries with 3 types of chronic conditions, and 232.7 per 1000 beneficiaries with 10 or more types of chronic conditions.

Recognizing that individuals with more chronic conditions are more likely to be hospitalized in general, we examined the relationship between the number of ACSC hospitalizations, the number of hospitalizations with preventable complications, and the number of inpatient hospitalizations for any condition. Both the percentage of total hospitalizations attributable to ACSCs and preventable complications remained relatively constant as the number of types of chronic conditions increased. The percentage of hospitalizations attributable to ACSCs ranged from 8.5% to 12.0%, and the percentage of hospitalizations with preventable complications ranged from 5.0% to 6.1%. However, when the Medicare beneficiary was used as the unit for comparison (not the hospitalization), a relationship between the probability of having a hospitalization for an ACSC or with a preventable complication and the number of types of chronic conditions was apparent. Only 10.4% of individuals without a chronic condition incurred an ACSC hospitalization, compared with 26.9% of individuals with 10 or more types of chronic conditions. Likewise, 6.3% of individuals without a chronic condition incurred a hospitalization with a preventable complication, compared with 19.9% of individuals with 10 or more types of chronic conditions.

Table 4 presents the results of multiple logistic regression used to explore the odds of incurring an inpatient admission for an ACSC or an inpatient hospitalization with a preventable complication given the covariates of age and sex. The odds of incurring an inpatient admission for an ACSC were 7.5 times greater among individuals with 1 chronic condition and 98.5 times greater among individuals with 4 or more types of chronic conditions in comparison to their peers without a chronic condition. Likewise, the odds of incurring an inpatient admission with a preventable complication increased with increasing numbers of types of chronic conditions from 6.0 times greater among individuals with 1 chronic condition to 91.4 times greater among individuals with 4 or more types of chronic conditions.
Our most important findings were the association between the number of types of chronic conditions and the likelihood of incurring inpatient admissions for ACSCs. After age and sex were controlled for, individuals with 4 or more chronic conditions were 99 times more likely to have incurred a hospitalization that could have been prevented with appropriate primary care. Hospitalizations for conditions that could be preventable with adequate ambulatory care are widely thought to be a sensitive indicator of adequate primary care. Prior studies that have evaluated predisposing risk factors for avoidable hospitalizations among the elderly population have primarily evaluated sociodemographic characteristics or the presence of a single heath condition and have relied on relatively small sample sizes. To our knowledge, this study is the first one that has evaluated risk for incurring inpatient admissions for ACSCs indicates hospitalizations for ambulatory care sensitive conditions; Preventable Complications, hospitalizations for preventable complications. Reference groups are as follows: chronic conditions, none; age, 65-69 years; and sex, male.

<table>
<thead>
<tr>
<th>No. of chronic conditions</th>
<th>ACSCs</th>
<th>Preventable Complications</th>
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<tbody>
<tr>
<td>1</td>
<td>7.49 (6.50-8.65)</td>
<td>6.02 (4.99-7.25)</td>
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<tr>
<td>2</td>
<td>18.10 (15.79-20.76)</td>
<td>13.60 (11.39-16.24)</td>
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<td>3</td>
<td>36.43 (31.81-41.73)</td>
<td>29.17 (24.49-34.75)</td>
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<td>≥4</td>
<td>98.52 (86.11-112.72)</td>
<td>91.35 (76.85-108.59)</td>
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Age, y

<table>
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<tr>
<th>Age (y)</th>
<th>Odds Ratio (95% Confidence Interval)</th>
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<tr>
<td>70-74</td>
<td>0.98 (0.95-1.02)</td>
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<tr>
<td>75-79</td>
<td>1.18 (1.14-1.21)</td>
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<td>80-84</td>
<td>1.58 (1.53-1.63)</td>
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<tr>
<td>≥85</td>
<td>2.49 (2.41-2.57)</td>
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Sex

<table>
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<tr>
<th>Sex</th>
<th>Odds Ratio (95% Confidence Interval)</th>
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<tr>
<td>Male</td>
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<tr>
<td>Female</td>
<td>0.77 (0.75-0.79)</td>
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</table>

*ACSCs indicates hospitalizations for ambulatory care sensitive conditions; Preventable Complications, hospitalizations for preventable complications. Reference groups are as follows: chronic conditions, none; age, 65-69 years; and sex, male.

Our findings confirm prior reports of the high prevalence of multiple chronic conditions among older populations and the disproportionate direct medical expenditures associated with treating individuals with multiple chronic conditions. Using administrative claims data from a nationally representative random sample of aged Medicare beneficiaries, we found that nearly two thirds of elderly beneficiaries had 2 or more types of chronic conditions and accounted for 95% of Medicare expenditures. Approximately one fourth of the beneficiaries were found to have 4 or more types of chronic conditions; these individuals collectively incurred nearly two thirds of the Medicare program expenditures. Some combinations of chronic conditions occur more frequently than would be expected. The extent to which this represents increased biological vulnerability to certain types of conditions among people with certain chronic conditions deserves exploration in future studies of comorbidity. Clinicians whose specialty focuses on these conditions need to be aware of the high proportion of their patients with multiple chronic conditions and to know how to coordinate their care with other clinical providers.

We compared our findings with those of other published studies that reported the prevalence of multiple chronic conditions. Despite wide variation in how chronic conditions were defined, in data sources, and in sample sizes, the prevalence of multiple chronic conditions among the elderly has been widely reported to exceed 60%. These prior reports are commensurate with our finding that 65% of Medicare beneficiaries have more than 1 chronic condition.

The finding that hospitalization rates for ACSCs, a marker for the adequacy of ambulatory care, are so strongly related to the number of chronic conditions suggests that individuals with multiple chronic conditions may be less likely to receive appropriate primary care that could forestall acute events requiring hospitalization. Results from this study are compatible with those from studies that have reported that Medicare beneficiaries frequently fail to receive necessary care in compliance with practice guidelines and that individuals of greater age and with greater comorbidity may be particularly susceptible to medical undertreatment. The finding that inadequate or inappropriate ambulatory care may result in greater risk for inpatient hospitalizations among seniors has particular significance given the frailty of this population and the resulting hazard of functional decline and reduced quality of life associated with inpatient hospitalization.

Our study has several limitations that merit discussion. The first concerns the adequacy of characterizing chronic conditions. In the absence of a widely accepted definition of chronic illness, we used a characterization from an existing case-mix system. However, there are likely to be conditions that may be chronic that were grouped into ADGs that were not defined as chronic in this study; these particularly include conditions for which management may be “discretionary” in the sense that some may merit interventions, whereas others may not. For example, uterine fibroids (leiomyomas) and other benign tumors might or might not merit medical attention and in that sense might or might not be considered a chronic condition. These types of conditions were not included as chronic in our study; to this end, our study reflects a conservative approach to defining chronic conditions and an underestimation of comorbidity.

A second limitation of this study, given the available data, is our inability to account for clinical severity of illness among patients within specific categories of types of chronic conditions. For example, we are not able to determine whether individuals with chronic conditions related to the kidney and urinary tract (MDC 11) who also have other types of chronic conditions have more severe kidney and urinary tract disease in comparison with individuals with chronic conditions only related to the kidneys and urinary tract. However, as previously noted, while not the primary intent, our classification of the number of types of chronic conditions by different organ system involvement inherently...
addresses the issue of severity of illness in the patient, if not the specific type of illness.

Third, expenditure estimates reflect only actual reimbursable services under the Medicare program and therefore are likely to underestimate the actual burden to individuals and their families. As a result, we were unable to identify numerous health services, out-of-pocket costs, and costs attributable to lost productivity and decrements in quality of life that are not reimbursable under the Medicare program. Fourth, the study is subject to biases contained within the data. Studies suggest that chronic conditions may in some cases be underreported on administrative claims data, particularly among inpatient hospitals. Moreover, to the extent that prevalence estimates rely on administrative claims, our prevalence estimates reflect treated prevalence among this population, and it is possible that individuals with chronic conditions who did not receive reimbursable medical care under the Medicare program were misclassified as having fewer chronic conditions than they actually had. Finally, given the lack of information on Medicare managed care, we are unable to generalize our findings to Medicare beneficiaries enrolled in managed care.

Our study also failed to control for social variables related to increased morbidity. Since prior studies have found a relationship between low socioeconomic status and increased risk of incurring an ACSC, it is possible that the findings reflect the effects of low socioeconomic status. However, the rates of comorbidity are so high as to make it unlikely that differences in socioeconomic status account for these findings.

These findings have policy implications for the Medicare program on several levels. One study estimated the potential cost savings to the Medicare program associated with reducing avoidable hospitalizations to be $9.3 billion in 1991. A recent national study, using data from the National Hospital Discharge Survey, found hospitalizations for avoidable conditions to have increased substantially between 1980 and 1998, with rates rising most dramatically among the population aged 65 years and older. If such events have increased among the elderly in recent years, as has been suggested, then Medicare expenditures associated with avoidable hospitalizations could be substantially greater today.

Results of this study have implications with regard to how quality of care among Medicare beneficiaries should be assessed, how benefits should be structured, and where quality assurance programs should be directed. These findings along with those of other studies showing the importance of primary care in the prevention of hospitalizations for ACSCs and the importance of coordination of care among individuals with chronic conditions make attention to adequacy of primary care essential for quality assessment efforts. Coordination of care, especially for patients with multiple chronic conditions, requires time and skill. Perhaps an explicit payment is necessary for physicians to perform this coordination-of-care function.

Our finding that the number of chronic conditions was associated with more hospitalizations with preventable complications suggests that individuals with multiple types of chronic conditions may be at greater risk for incurring complications associated with inpatient care. Although we might have expected the rate of preventable complications per hospitalization to be higher among Medicare beneficiaries with multiple types of chronic conditions, it is possible that we did not find this to be the case because the complications are discrete and serious unitary events that would not necessarily occur more than once during a hospitalization, regardless of its length. Moreover, the type of services may differ for patients of different ages; if surgery is performed less frequently among older individuals, then as a group they would have fewer complications from surgery. Approximately 5% of hospitalizations were found to have a preventable complication—a percentage that is consistent with estimates from other studies, which found that injuries resulting from medical management occurred in 2.9% to 3.7% of inpatient admissions among all age groups (not just the elderly) and that adverse drug events occur in 6% to 7% of non-obstetric hospitalizations.

Policy makers in government agencies who are responsible for monitoring clinical protocols and for developing medical guidelines should acknowledge the existence of significant numbers of individuals who are affected not just by 1 chronic condition but by multiple co-occurring conditions. Food and Drug Administration approval for new drugs is generally based on clinical trials of individuals who meet strict exclusion criteria, typically excluding patients with a second chronic condition. Consequently, the effectiveness of new drugs among individuals with multiple chronic conditions may not be evaluated prior to market. Similarly, clinical treatment guidelines developed by the National Institutes of Health and the Agency for Healthcare Research and Quality typically fail to recognize and incorporate protocols for the treatment of individuals with multiple chronic conditions. At a minimum, the validity of findings from single-disease interventions and clinical trials may not hold in a practical setting in which patients have multiple conditions; in the worst case, protocols developed for the treatment of a single disease may be contraindicated among patients with specific co-occurring diseases.

Accepted for publication May 2, 2002.

This study was supported in part by Partnership for Solutions, a national program of The Robert Wood Johnson Foundation, Princeton, NJ.

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