Drug-Related Morbidity and Mortality: A Cost-of-Illness Model

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BACKGROUND:

Preventable drug-related morbidity and mortality represent a serious medical problem that urgently requires expert attention. The costs to society of the misuse of prescription medications, in terms of morbidity, mortality, and treatment, can be immense. To date, research has primarily documented increased rates of hospitalization secondary to medication noncompliance and/or adverse drug effects.

OBJECTIVES:

To develop a conceptual model of drug-related morbidity and mortality, and to estimate the associated costs in the ambulatory setting in the United States.

METHODS:

A probability pathway model was developed to estimate the cost of drug-related morbidity and mortality in the United States. Pharmacist practitioners were surveyed to determine conditional probabilities of therapeutic outcomes owing to drug therapy. Health care use and associated costs owing to negative therapeutic outcomes were estimated.

RESULTS:

Drug-related morbidity and mortality was estimated to cost \$76.6 billion in the ambulatory setting in the United States. The largest component of this total cost was associated with drug-related hospitalizations.

When assumptions of the model were varied, the estimated cost ranged from a conservative estimate of \$30.1 billion to \$136.8 billion in a worst-case scenario.

CONCLUSIONS:

The cost of drug-related morbidity and mortality in the ambulatory setting in the United States is considerable and should be considered in health policy decisions with regard to pharmaceutical benefits. Policies and services should be developed to reduce and prevent drug-related morbidity and mortality.

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When medications are prescribed for patients for the treatment of disease, the full intent of all parties involved should be the achievement of an optimal therapeutic outcome. Optimal therapeutic outcome has been defined as an absence of drug-related problems (DRPs).¹ A DRP is defined as an event or circumstance that involves a patient's drug treatment that actually, or potentially, interferes with the achievement of an optimal outcome. Eight general categories of DRPs have been identified (Table 1).^{1,2}

Unresolved or unrecognized DRPs may manifest as drug-related morbidity, which has been described as the phenomenon of therapeutic malfunction or miscarriage—the failure of a therapeutic agent to produce the intended outcome.¹ If left untreated, drug-related morbidity may ultimately lead to drug-related mortality. While it is recognized that some drug-related morbidity and mortality is owing to patient idiosyncrasy, and therefore unavoidable, there is a

considerable body of literature that suggests that a large proportion of drug-related morbidity is preventable.¹⁻⁵

Manasse^{3,4} used the term "drug misadventuring" to describe these inappropriate outcomes, and he proposed that the problem must be viewed as one of public policy. Manasse suggested that the costs to society of the misuse of prescription medications, in terms of morbidity, mortality, and treatment, can be immense. He also suggested that the new policy decisions must be constructed in the best interest of the patient. The extent and cost of drug-related morbidity and mortality are of great importance to health care practitioners, administrators, patients, and society as a whole.

Estimates of personal health expenditures for prescription medications in 1994 have exceeded \$73 billion.⁶ Recent literature has indicated that the substantial costs associated with inappropriate drug-use behavior may even exceed these initial expenditures for drug therapy.^{7,8} To

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Table 1. Drug-Related Problems^a

Problem	Description
Untreated indication	The patient has a medical problem that requires drug therapy but is not receiving a drug for that indication.
Improper drug selection	The patient has a drug indication but is taking the wrong drug.
Subtherapeutic dosage	The patient has a medical problem that is being treated with too little of the correct drug.
Failure to receive drugs	The patient has a medical problem that is the result of not receiving a drug (e.g., for pharmaceutical, psychological, sociological, or economic reasons).
Overdosage	The patient has a medical problem that is being treated with too much of the correct drug (i.e., toxicity).
Adverse drug reactions	The patient has a medical problem that is the result of an adverse drug reaction or adverse effect.
Drug interactions	The patient has a medical problem that is the result of a drug-drug, drug-food, or drug-laboratory interaction.
Drug-use without indication	The patient is taking a drug for no medically valid indication.

^a Data from Hepler and Strand¹ and from Strand et al.²

date, research has primarily documented increased rates of hospitalization secondary to medication noncompliance and/or adverse drug effects.⁸⁻¹⁴ Sullivan et al.⁸ estimated the direct medical costs associated with hospitalizations owing to medication noncompliance to be \$8.5 billion. The authors suggested that an additional \$17–24 billion would be incurred as indirect costs. A more recent estimate has put the direct costs of noncompliance at greater than \$50 billion, with an additional \$50 billion in indirect costs.¹⁵

While noncompliance and resultant hospitalizations are certain to account for a large proportion of DRPs and associated direct medical costs, respectively, limiting an analysis to these issues alone would surely underestimate the true extent of drug-related morbidity and mortality. Likewise, direct costs of hospitalizations would also underestimate the economic impact of the "illness," as only the direct costs associated with those misadventures of sufficient severity to warrant hospital admission would be captured. What of the costs associated with outpatient visits? Or of return visits to the pharmacy? Or additional treatment of any new medical problems? An analysis of the direct costs of illness of drug-related morbidity and mortality should take into consideration these aspects of management of the "disease." To date, there have been no reports, of which we are aware, of the total economic impact of such drug misadventuring, and further analysis is warranted.⁹

Recent debates in the health and public policy arena have

considered the impact of a pharmaceutical benefits plan that would include coverage of products and services. The DRPs and drug misadventuring should be considered in these policy issues. An estimate of the costs associated with drug-related morbidity and mortality will aid in the policy-making decisions area. In an attempt to address this issue, the present investigation was undertaken. Two objectives were set: (1) to develop a conceptual model of therapeutic outcomes that may result from drug therapy; and (2) to estimate the magnitude of the cost of drug-related morbidity and mortality in the United States.

(See pages 43-45 for Methods.)

ESTIMATES OF THERAPEUTIC OUTCOMES

According to the panel members, $23.4 \pm 13.2\%$ (mean $\pm$ SD) of patients who receive drug therapy would experience a TF owing to DRPs; $10.5 \pm 5.4\%$ would experience an NMP, and $6.5 \pm 4.1\%$ would experience a combination of a TF and an NMP. The panel members estimated that less than 60% of patients who were receiving medication would have an absence of DRPs (i.e., an optimal outcome).

Estimations of the health care resources that would be used in the management of negative therapeutic outcomes differed for the three possible outcomes. Panel members estimated that approximately 8–18% of negative therapeutic outcomes would not require further attention of a health care professional, but 15–23% of patients would see a physician, and 42–49% would require further prescription medication. Negative therapeutic outcomes would lead to an urgent care visit or emergency department visit for 12–19% and 6–12% of patients, respectively. Four panel members did not provide a response to the urgent care visit item, as this was a service that was unfamiliar to those panel members in their practice setting. Because of these missing data, the urgent care visit outcomes were collapsed into physician visits such that the probabilities could be inserted into the decision analysis model.

The panel also estimated that 5% of patients who experience a TF or in whom an NMP would develop would be admitted to a hospital; a combination of negative therapeutic outcomes would lead to a higher percentage of patients being admitted to a hospital, that is, approximately 9%. Most panel members estimated that less than 1% of negative therapeutic outcomes would result in an admission to a long-term care facility. Death was estimated to occur in less than 1% of patients who were receiving medications.

COST OF DRUG-RELATED MORBIDITY AND MORTALITY

Folding back the decision tree, to merge the conditional probabilities and costs of all pathway outcomes, produced the mean aggregate cost that was associated with health care encounters. The expected cost of a physician visit was \$194

Table 2. Drug-Related Morbidity and Mortality Cost Definitions^a

Pathway outcome	Initial treatment (\$)		Cost of negative therapeutic outcome (\$)					Total Pathway Cost (\$)
	Physician visit ¹⁶	Drug ^{11,b}	Physician Visit	Drug	ED Visit	Hospital Admission ¹⁹	LTC Admission ^{20,21}	
Optimal outcome	64.50	25.32						89.82
TF								
No treatment	64.50	22.79						87.29
Physician visit	64.50	22.79	64.50					151.79
Additional treatment	64.50	22.79	64.50	25.32				177.11
ED visit	64.50	22.79			312.00			399.29
Hospital admission	64.50	22.79				5415.00		5,502.29
LTC admission	64.50	22.79					4571.47	4,858.76
Death	64.50	22.79				5415.00		5,502.29
NMP								
No treatment	64.50	25.32						89.82
Physician visit	64.50	25.32	64.50					154.32
Additional treatment	64.50	25.32	64.50	25.32				179.64
ED visit	64.50	25.32			312.00			401.82
Hospital admission	64.50	25.32				5415.00		5,504.82
LTC admission	64.50	25.32					4571.47	4,661.29
Death	64.50	25.32				5415.00		5,504.82
TF/NMP								
No treatment	64.50	22.79						87.29
Physician visit	64.50	22.79	64.50					151.79
Additional treatment	64.50	22.79	64.50	25.32				177.11
ED visit	64.50	22.79			312.00			399.29
Hospital admission	64.50	22.79				5415.00		5,502.29
LTC admission	64.50	22.79					4571.47	4,858.76
Death	64.50	22.79				5415.00		5,502.29
No drug therapy	64.50							64.50

^a ED indicates emergency department; LTC, long-term care; TF, treatment failure; and NMP, new medical problem.

^b Estimated drug cost for TF and TF/NMP are reduced by 10% to reflect rate of new prescriptions never filled.

Table 3. Health Care Utilization and Cost for Drug-Related Morbidity and Mortality in the United States^a

	No. of events	Cost (\$, in thousands) ^b
Physician visits	115,654,949	7,459,744
Additional prescriptions	76,347,604	1,933,121
ED visits	17,053,602	5,320,723
Hospital admissions	8,761,861	47,445,477
LTC admissions	3,149,675	14,398,644
Deaths	193,815	
Total		76,557,711

^a ED indicates emergency department; LTC, long-term care.

^b Costs may not total correctly because of rounding off.

(95% confidence interval, \$154 to \$234). This cost figure has no intrinsic value, but is simply the weighted mean cost of the entire pathway model (i.e., all possible outcomes).

When therapeutic outcomes owing to drug therapy were modeled for the ambulatory population of the United States, the estimated cost that was associated with the management of drug-related morbidity and mortality was \$76.6 billion, annually (Table 3). The largest component of the total cost comprised drug-related hospitalizations, that is, an estimated 8.76 million admissions at a cost of \$47.4 billion, annually, or approximately 62% of the total cost. Based on 31.1 million hospital admissions in 1992,¹⁹ the number of admissions that was

estimated from the model suggested that 28.2% of all hospital admissions were a result of drug-related morbidity and mortality.

Admissions to long-term care facilities represented the second largest component of the total cost of illness, with 3.15 million admissions at a cost of \$14.4 billion (Table 3). Visits to the physician resulting from DPRs would exceed 115 million, and these visits would cost nearly \$7.5 billion, while an additional 76.3 million prescriptions would be required to resolve TFs and NMPs, adding \$1.93 billion to the cost. This represents 17.3% of all physician office visits,²⁴ and 8.2% of all prescriptions¹⁶ that were estimated for 1992. The number of emergency department visits that resulted from drug-related morbidity represented 18.9% of an estimated 89.8 million emergency department visits in 1992.²⁶

SENSITIVITY ANALYSES

When the probabilities of negative therapeutic outcomes were varied throughout the range provided by the panel, the costs that were associated with drug-related morbidity and mortality ranged from \$30.1 billion for the more conservative end of the range of negative therapeutic outcomes to \$136.8 billion in a worst-case scenario. When the assumed rate of initial noncompliance was increased to 25%, the estimated cost

Table 4. Direct Costs of Select Conditions in the United States

Source	Condition (year)	Cost (\$, billions)
Wolf and Colditz, ²⁷ 1994	Non-insulin-dependent diabetes (1990)	15.5
	Obesity (1990)	45.8
American Diabetes Association, ²⁸ 1993	Diabetes (1992)	45.2
American Heart Association, ²⁹ 1993	Cardiovascular disease (1992)	117.0
Present study	Drug-related morbidity and mortality (1994)	76.6

that was associated with DRPs increased to \$128.2 billion.

The analysis was sensitive to the cost assumptions that were included in the model, particularly for costs of hospital and long-term care admissions. A cost of treatment of \$37.9 billion was estimated when the cost of hospitalization was reduced to \$1,000 per admission; the figure increased to \$204.3 billion when a cost of \$20,000 per admission was used. The hospital costs that were chosen for this sensitivity analysis were an arbitrary range.

The cost of a long-term care admission in the base-case analysis was based on the reported median length of stay of 82 days. When an average length of stay (401 days)²¹ was used, the estimated cost of a long-term care admission was \$22,355. The inclusion of this figure in the model produced a cost of illness of \$132.6 billion.

COMMENT

Causes of preventable drug-related morbidity and mortality may be a result of inappropriate behavior, be it noncompliance by the patient, or inappropriate prescribing and/or monitoring by health care professionals. As such, drug-related morbidity and mortality could be considered a "behavioral disease." With this view, an estimate of the economic impact of the "disease" could be assessed by using cost-of-illness methods. Analyses to assess the economic impact of illnesses on society have been performed since the mid-1960s,^{27,28} with most of the major medical conditions being assessed at one time or another.²⁹ While some economists believe that cost-of-illness studies provide little information with regard to resource allocation decisions,³⁰⁻³³ one important role for these analyses is as a baseline assessment, against which new programs or policies can be evaluated.^{28,29}

The cost of illness associated with DRPs estimated in this analysis would serve to strengthen the suggestion of Manasse^{3,4} that drug-related morbidity and mortality is a serious medical problem and should be considered an issue of public policy. The analysis presents a figure that can now be debated, but it is clear that the problem is more than a minor concern for the health of the nation.

To put the results of this analysis in perspective, the cost-of-illness figures could be compared with the estimated costs

Figure 1. Drug-Related Morbidity and Mortality

TF indicates treatment failure; NMP, new medical problem; ED, emergency department; and LTC, long-term care.

of other conditions in the United States (Table 4). For example, obesity was estimated to cost \$45.8 billion in direct costs in 1990.³² All diabetes care has been estimated to cost \$45.2 billion, annually.³³ Noninsulin-dependent diabetes mellitus care cost \$15.5 billion in 1990.^{32,33} The treatment of cardiovascular disease have been estimated to cost \$117–\$154 billion.^{32,34} Our results indicate that drug-related morbidity and mortality should be considered one of the leading disease in terms of resources consumed.

As stated earlier, the cost estimations made in this analysis were limited to the direct costs of managing drug-related morbidity and mortality. A more complete estimation (i.e., a societal perspective) of the costs associated with this health

METHODS: CONCEPTUAL MODEL FOR DRUG-RELATED MORBIDITY AND MORTALITY

A probability pathway model for drug-related morbidity and mortality was developed (Figure) that was based primarily on the DRPs and negative therapeutic outcomes as described in recent literature.^{1,2} Any one, or a combination, of these DRPs may occur in any given patient, and may lead to treatment failures (TFs) and new medical problems (NMPs) as possible negative outcomes. An absence of DRPs would represent the optimal therapeutic outcome. These outcomes were used as the basis for the conceptual model. However, because a TF and an NMP may occur in the same patient as a result of a number of DRPs, a third negative therapeutic outcome was included (i.e., a combination of a TF and an NMP) to make the possible therapeutic outcomes mutually exclusive. An example of a TF due to a DRP would be an unresolved infection following improper antibiotic selection; an NMP might be a rash that develops after starting antibiotic therapy. A combination of negative therapeutic outcomes might occur when an infection is treated with an improper antibiotic, which causes a rash.

For patients experiencing a TF or an NMP due to DRPs, it was thought that one of eight subsequent events could occur as follows: (1) a revisit with a physician, (2) a further prescription medication, (3) an urgent care visit, (4) an emergency department visit, (5) a hospital admission, (6) a

long-term care facility admission, (7) death, or (8) no further attention of a health care professional. These eight events were defined as the end points, or final resolutions, of negative therapeutic outcomes, as such, to be mutually exclusive (i.e., their respective probabilities would sum to 1.0). For example, with regard to event 2, a further prescription medication implies a preceding physician visit, so that event 1 then represents patients who revisited a physician but had no further treatment.

While the morbidity and mortality and associated costs, resulting from the use and abuse of illicit drugs, are recognized as a substantial problem, an attempt to assess the economic impact of such behavior was considered to be beyond the scope of this project. It should also be noted that DRPs and associated costs were estimated for ambulatory settings and, such, did not include those that may occur in institutional settings (e.g., hospitals, long-term care facilities).

To determine estimates of the probabilities of negative outcomes of drug therapy, a panel of pharmacists was surveyed. These individuals were selected based on their extensive clinical practice in an ambulatory setting and recognition as leaders in pharmacy practice in the United States. The primary goals of each of their clinical practices were the identification, resolution, and prevention of DRPs. A letter of invitation was sent to 18 potential panel members; this letter explained the objectives of the project. Invitation letters were followed by a telephone call to confirm panel participation and to schedule a 30-minute telephone interview. Telephone

problem would include some consideration of the indirect costs, that is, the economic impact of lost productivity as a result of morbidity and mortality.^{27,28} Rice et al.³⁰ indicated that, overall, the indirect cost of illnesses exceed the direct costs. Sullivan et al.⁸ suggested that the indirect costs associated with medication noncompliance was an additional \$17–\$25 billion, that is, two to three times the estimated direct costs. Applying this ratio to the estimates calculated in the present analysis would suggest that the total cost of all preventable drug-related morbidity and mortality to the United States, in terms of health care costs as well as lost productivity, would amount to \$138–\$182 billion.

The limitations to the estimates made from the model should be obvious. The model developed for this project was conceptual, and the probabilities attached to therapeutic outcomes, as well as the cost figures assigned to the outcomes, were estimations. As such, the cost of illness is only an estimate. However, the sensitivity of the model to the panel's estimations was extensively tested through sensitivity analysis, and the cost definitions used in the model were transparent.

Of primary concern to many readers will be the appropriateness of the chosen panel members. The panel members were composed of expert practicing pharmacists, with no representatives from the physician or nursing community. As such, the estimations made by the panel members may be

viewed by some as biased. A panel member composed of other health care professionals might help to reduce potential bias. However, the difficulty then lies in the identification of such a panel member; for example, should physicians be general practitioners, specialists, or clinical pharmacologists? In addition, the practitioners included in the panel were trained specifically to identify, prevent, and resolve DRPs, whereas other health care professions do not have the same focus.

If the probabilities of therapeutic outcomes estimated by the expert panel are accepted as "best estimates," and the monetary values assigned to outcomes are also considered appropriate, then it may be the model within which these figures were used that may be questioned. Was it the correct model? Were important outcomes not included? These questions are more difficult to address.

Appropriateness of the model may be judged by comparing the results of this analysis with findings from previous reports of drug-related morbidity and mortality. Our estimates appear to be in line with those of other reports. The estimated number of deaths owing to DRPs in this analysis ranged from 79,159 to 198,815 deaths. Tally and Laventurier⁵ estimated that 140,000 patients died in the United States because of adverse drug reactions in 1971.

Several studies have attempted to quantify the rate of drug-related hospital admissions. Reported rates have ranged

interviews were scheduled for 15 panel members; three potential panel members were unable to be reached by telephone.

All panel members were currently practicing; advanced pharmacy degrees were held by nine panel members (Pharm.D. [$n = 6$], M.Sc. [$n = 2$], and Ph.D. [$n = 1$]). Three panel members had advanced degrees in public health (M.P.H. [$n = 2$] and Dr.P.H. [$n = 1$]). Most panel members (nine of 15) indicated that their primary practice setting was ambulatory; four panel members characterized their practice setting as part of a managed care organization, and two indicated long-term care as their primary setting.

A standardized interview form was developed based on the cost-of-illness model described above. Respondents were instructed to provide their estimate of the likelihood of the three negative therapeutic outcomes owing to drug therapy in patients in a typical ambulatory health care setting in which they were not available to provide their current level of clinical practice. Respondents were then asked to estimate the percentage of patients who experienced each of the three negative therapeutic outcomes that would require further attention and utilization of additional health care resources. All items were open-ended questions. To facilitate the scheduled telephone interviews, the interview form was faxed to all participating panel members approximately four to five days before their scheduled interviews. Respondents were also provided with a schematic diagram of the pathway model (Figure 1).

from 2.3%³⁵ to 27.3%.¹¹ Meta-analysis, performed by Sullivan et al.⁸, resulted in a weighted estimate of 5.3% of hospitalizations being due to noncompliance. More recently, Einarson⁹ reported the results of a meta-analysis of studies that dealt with hospitalizations due to reactions that occurred while the patient was taking medications appropriately or to reactions that resulted from noncompliance or unintentionally inappropriate drug use. The analysis indicated that a weighted rate of 5.1% of hospital admissions were owing to these causes.

According to the model in the present analysis, the number of drug-related hospital admissions ranged from 3.5–8.8 million annually, representing 11.3–28.2% of estimated hospital admissions in 1992.¹⁹ These estimates appear to be higher than those in previous reports. However, those previous estimates were focused on hospital admissions that resulted from noncompliance alone, or as the result of an adverse drug reaction. Because the present estimate included negative therapeutic outcomes owing to all types of DRPs, the estimated number of hospital admissions would be expected to be greater.

In addition, documentation drug-related hospital admissions is difficult, and it is possible that many hospital admissions are the result of DRPs that go unrecognized. For example, a patient with insulin-dependent diabetes who is admitted to a hospital with diabetic ketoacidosis may be more

COST DEFINITIONS

The cost-generating components of therapeutic outcomes were identified, and these components were assigned a monetary value. Monetary values for relevant therapeutic outcomes were identified from previous published research reports and from available statistical reports (Table 2).^{16–21} The perspective taken was that of a third-party payer, such as a managed care organization. Only those health care costs that were directly associated with the treatment of preventable drug-related morbidity and mortality were estimated.

Costs associated with death owing to DRPs were difficult to estimate. Because the perspective undertaken for the present investigation was that of third-party payer, the indirect costs of lost productivity to society were not included. However, it seemed likely that the health care system would incur some costs associated with deaths owing to DRPs. For the base-case analysis of the present investigation, it was assumed that deaths owing to negative therapeutic outcomes were preceded by a hospital admission.

Because the ultimate outcome, or resolution, of drug-related morbidity and mortality may require a series of health care encounters, the costs associated with the final pathway must reflect all previous health care encounters (Table 2). For example, additional prescription therapy would imply a preceding prescriber contract. As such, the cost of managing a TF owing to a DRP may include the cost of an initial physi-

likely to be classified as a drug-related admission than an asthmatic patient who has underutilized his or her inhaled corticosteroids. As a result, the number of drug-related admissions documented in previous reports may underestimate the problem.

An additional point that should be considered in the evaluation of this model and the cost estimates in the model relates to high-risk groups. Of particular importance are elderly patients who would be considered to be at high risk of DRPs and negative therapeutic outcomes for a number of factors that are unique to that age group, including the physiologic effects of aging on the disposition of drugs, multiple disease processes, and multiple, concurrent drug therapies.³⁶ The estimations of likelihood of negative therapeutic outcomes made by the expert panel members for this analysis were made for the general ambulatory population. If elderly patients were to be considered alone, the risks would have been greater.

Highlighted by the results of this analysis is the serious nature of all drug therapy. In all estimations, despite the best efforts to achieve optimal therapeutic outcomes by players on the health care team, there remains a considerable expense (and a sizable number of deaths resulting from drug therapy) that might be considered unavoidable. As Manasse³ indicated, "the reality of introducing a chemical agent into the body is accompanied predictable (and often unpredictable) elements

cian visit, an initial prescription for the offending drug, and then a revisit to the physician. The revisit then may or may not lead to an additional prescription. Alternatively, a new medical problem may require hospitalization for proper treatment, and so the associated costs should include not only the cost of the hospital stay but also the cost of the initial physician visit and prescription.

Conditional probabilities for all therapeutic outcomes, based on responses from the panel members, were inserted into the decision analysis model. The expected cost of drug therapy following a health care encounter under each scenario were calculated by "folding back" the decision tree. Folding back is the process of multiplying the cumulative conditional probabilities by the cost of the outcomes, and then summing these values to determine the mean aggregate cost of the scenario.²² The expected cost is not a prediction of what will actually occur but is simply a weighted average of the possible outcomes.²³

COST-OF-ILLNESS ANALYSIS

Health care utilization and associated costs owing to negative therapeutic outcomes in ambulatory populations were estimated. The number of revisits to physicians, additional prescriptions, long-term care admissions, and deaths owing to negative therapeutic outcomes were calculated by multi-

of risk" and it is "simply unrealistic to contemplate the ability to take 'the risk out of risk' with respect to drug development and consumption." However, it is perhaps possible that, given the opportunity to reduce the "preventable" component of drug-related morbidity and mortality, the proportion that is currently considered "unavoidable" may also be reduced.

Preventable drug-related morbidity and mortality represents a serious medical problem that urgently requires expert attention.^{1,3,4} The extent to which negative therapeutic outcomes can be minimized would represent the value of that expert attention. Given the estimates of the costs associated with DRPs, even a 10% reduction in this inappropriate behavior could lead to substantial savings to the health care system and to society as a whole.

Pharmaceutical care may provide the basis on which health care professionals can make that impact. Pharmaceutical care is a practice philosophy that was put forth by Hepler and Strand¹ and embraced by most pharmacy practice organizations.³⁷⁻³⁹ It is defined as the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve the patient's quality of life.¹ The desired outcomes are stated as (1) cure of a disease, (2) elimination or reduction of a patient's symptoms, (3) arresting or slowing of a disease process, or (4) preventing a disease or symptom. Pharmaceutical care is patient-oriented, and it involves the implementation and monitoring of a therapeutic plan that is designed to achieve these outcomes.¹ The presence of DRPs lead to less

plying the cumulative conditional probabilities for each outcome derived from the decision analysis model by the assumed number of physician visits. The direct cost of treating drug-related morbidity and mortality in the United States was then estimated by multiplying the number of health services used as a result of negative therapeutic outcomes, by the estimated unit cost of each service. Calculations were made under the following assumptions: (1) an estimated 669,689,000 physician office visits annually;²⁴ (2) 63.3% of office visits result in at least one medication ordered or supplied by the physician;²⁴ (3) 10% of initial prescriptions are never filled,⁷ leading to TFs or a combination of a TF and an NMP.

SENSITIVITY ANALYSES

Because the data used in the cost-of-illness model were based on estimations by the panel members, a series of one-way sensitivity analyses²⁵ were performed for plausible ranges in the following variables: (1) the ranges in likelihood's of negative therapeutic outcomes indicated by the panel members, (2) all cost estimates included in the model, and (3) estimates of initial noncompliance with prescriptions.

All probability calculations, cost analyses, and sensitivity analyses were performed by using Decision Analysis by TreeAge (DATA)v2.523 and Microsoft EXCEL v4.0 (Microsoft Corp., Redmond, Wash.).

than optimal therapeutic outcomes. A major function of pharmaceutical care then is to identify, prevent, and resolve DRPs.

While not addressed in this analysis, the effect of drug-related morbidity and mortality on the quality of life of patients might also be considered. The very definition of pharmaceutical care is an intended improvement of a patient's quality of life, presumably through the cure or arrest of a disease and/or an elimination of symptoms.¹ From this, the provision of pharmaceutical care to the ambulatory medical population of the United States would not only lead to a substantial cost avoidance but it might also be expected to lead to an improvement in the general well-being and health status of the population.

The development and refinement of the pharmaceutical care concept represent somewhat of an "awakening" for the profession of pharmacy. While many pharmacists have provided services that constituted pharmaceutical care, the overwhelming sentiment in the pharmacy literature is that pharmaceutical care is being provided by only a relatively small proportion of pharmacists in select practice settings. Primary reasons for this include a lack of education, training, and support, a lack of resources, and a lack of a reimbursement system for those services.⁴⁰

Pharmaceutical care holds tremendous opportunity for pharmacists to realize their full potential as members of the health care team.¹ However, the responsibility of pharmaceutical care of patients cannot be held by a single profession. In-

stead, it is perhaps the bridge that is necessary for the interdisciplinary team approach to patient treatment. By definition, pharmaceutical care engenders a multidisciplinary approach to patient treatment. While the literature with regard to pharmaceutical care has been largely contained in the pharmacy community, it cannot truly be provided in isolation of medical and nursing care. The responsible provision of drug therapy involves proper diagnosis, prescribing, and monitoring.

For most drug therapies, diagnosis and prescribing remain the physician's responsibility; nurses have played, and should continue to play, a vital role in patient monitoring. Based on their training and knowledge base, pharmacists might be expected to provide the bulk of pharmaceutical care, proper diagnosis and prescribing are required to minimize preventable drug-related morbidity and mortality. Pharmaceutical care should be provided to patients in the same way the medical and nursing care are attempts to achieve optimal therapeutic outcomes.

Hepler and Strand¹ indicated that "the empirical bases of pharmaceutical care suggest that there may be a substantial overlap between clinical effectiveness and cost-effectiveness." However, despite an implicit cost-effectiveness, the costs and benefits of the provision of pharmaceutical care should be made explicit to convince policymakers of the value of enhanced pharmacy services. In times of limited resources allocation, it is necessary to justify the economic outlay demanded by new or enhanced programs. The provision of

pharmaceutical care should be no different.

A body of empirical research exists that has demonstrated the benefits of pharmaceutical care, and this literature is expanding. Enhanced pharmacy services have led to improved detection, and substantial reductions in DRPs, as well as reduced health care use leading to substantial cost-savings.^{18,41-51} These benefits have been realized in diverse settings and patient populations. These reports, however, have been limited to retrospective reviews or controlled, prospective reviews of short duration and have centered on inpatient hospital care and services. Prospective, controlled trials of enhanced pharmacy services in an ambulatory setting are not yet available in the literature.

In a recent editorial, Dukes⁵² suggested that, to some extent, any monetary measures of adverse effects of drugs will be artificial and incomplete. We do not contend that this analysis conclusively determined the total cost of drug-related morbidity and mortality in the United States. Rather, we attempted to make estimates within a conceptual model that can be further developed and refined. The model should be tested in real-life settings, in specific populations, in geographic regions, or in integrated health care settings, and it should be modified as necessary. The frequency of, and cost of drug-related morbidity and mortality in the ambulatory setting in the United States is considerable, and this cost should be considered in health policy decisions with regard to pharmaceutical benefits. ■

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