Drug-Related Morbidity and Mortality: Updating the Cost-of-Illness Model

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Objective: To update the 1995 estimate of $76.6 billion for the annual cost of drug-related morbidity and mortality resulting from drug-related problems (DRPs) in the ambulatory setting in the United States to reflect current treatment patterns and costs. ***Design:*** For this study, we employed the decision-analytic model developed by Johnson and Bootman. We used the model's original design and probability data, but used updated cost estimates derived from the current medical and pharmaceutical literature. Sensitivity analyses were performed on cost data and on probability estimates. ***Setting:*** Ambulatory care environment in the United States in the year 2000. ***Patients and Other Participants:*** A hypothetical cohort of ambulatory patients. ***Main Outcome Measures:*** Average cost of health care resources needed to manage DRPs. ***Results:*** As estimated using the decision-tree model, the mean cost for a treatment failure was $977. For a new medical problem, the mean cost was $1,105, and the cost of a combined treatment failure and resulting new medical problem was $1,488. Overall, the cost of drug-related morbidity and mortality exceeded $177.4 billion in 2000. Hospital admissions accounted for nearly 70% ($121.5 billion) of total costs, followed by long-term-care admissions, which accounted for 18% ($32.8 billion). ***Conclusion:*** Since 1995, the costs associated with DRPs have more than doubled. Given the economic and medical burdens associated with DRPs, strategies for preventing drug-related morbidity and mortality are urgently needed.

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When people use medications, any number of outcomes are possible. Most commonly, the patient benefits from pharmacotherapeutic interventions; however, adverse events, ranging from minor side effects to death, may occur. Any deviation from the intended beneficial effect of a medication results in a drug-related problem (DRP).[1] One or more DRPs may develop in a given patient after the initial drug therapy.

Researchers have shown that costs associated with DRPs exceed the expenditures for initial drug therapy; that is, the total cost of drug-related morbidity and mortality exceeds the cost of the medications themselves.[2,3] DRPs are increasingly recognized as a serious and urgent—but largely preventable—medical problem.

In 1989 Manasse proposed that, because DRPs are of immense importance to the whole of society as well as to health care providers, administrators, and patients, they should be addressed as a matter of public policy.[4,5] In the following 6 years, research focused primarily on documenting increased rates of hospitalization resulting from nonadherence to prescribed medication regimens and/or adverse drug effects.[6–17]

Johnson and Bootman,[1] in a widely cited study published in 1995, detailed a cost-of-illness model they developed to address drug-related morbidity and mortality in the ambulatory care setting in the United States. Using a structure originally developed by Hepler and Strand,[18,19] Johnson and Bootman developed a decision-analytic model for eight possible negative outcomes of drug therapy:

- Untreated indication
- Improper drug selection
- Subtherapeutic dosage
- Failure to receive drugs
- Overdosage
- Adverse drug reactions
- Drug interactions
- Drug use without indication

The model included probabilities and costs associated with the following therapeutic outcomes, any one of which could result from the above eight possibilities:

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- No treatment necessary
- Physician visit
- Additional treatment
- Emergency department visit
- Hospital admission
- Long-term care facility admission
- Death

On the basis of data obtained in the early 1990s, Johnson and Bootman estimated that, on average, $76.6 billion ($30.1 billion to $136.8 billion) is spent annually in the ambulatory setting in the United States to resolve DRPs, with drug-related hospitalizations being the largest component of this cost.[1] At the time of the study, their model seemed appropriate, based on an assessment of previously published findings.[20] The model did have some acknowledged weaknesses, however. Members of the expert panel Johnson and Bootman consulted used their "best estimates," rather than actual empirical data, in determining the probabilities of therapeutic outcomes; monetary values were extrapolated from previously published research reports and available statistical reports and used to estimate mean costs.

As recent history indicates, health care trends change quickly. Therefore, some of the data used in the 1995 study, and hence the estimates developed, are outdated. Fortunately, empirical data are available for use with cost-of-illness models. Several studies published since 1995 have, for example, investigated the cost of drug-related morbidity and mortality in specific patient populations.[21–24] Other additions to the literature have examined the incidence and probabilities of drug misadventures.[25–31]

Objective

Our purpose for conducting this study was to update the 1995 estimate of $76.6 billion for the annual cost of drug-related morbidity and mortality resulting from DRPs in the ambulatory setting in the United States to reflect current treatment patterns and costs.

Methods

We duplicated the 1995 analysis using Johnson and Bootman's original decision-analytic model[1] and full data set (obtained with the cooperation of the original authors) on which the publication and its preceding report were based.[32] We did this to ensure we fully understood the mathematical calculations and decision analyses performed during the previous study before we made any attempts to reassess them. We investigated the possibility that the values for the following variables had changed:

- Initial treatment costs, such as those for a physician visit and drugs
- Costs of negative therapeutic outcomes, such as additional physician visits, more drugs, emergency department (ED) visits, hospital admissions, and long-term-care (LTC) admissions
- Costs of nonnegative-outcome treatment failures (TFs) or new medical problems (NMPs)
- Total pathway costs
- Outcome probability estimates for each of the pathways.

Data Selection and Collection

The original study used a panel of clinical experts to collect data on therapeutic outcomes, resource use, and probabilities associated with the eight potential DRPs.[18,19] The original cost data were collected from a variety of nationally representative data sources. Using data published since the 1995 study, we updated these values for the present study and adjusted to May 2000 dollars using the Consumer Price Index.[33] When we could not find more recent data, we used the Johnson and Bootman data.

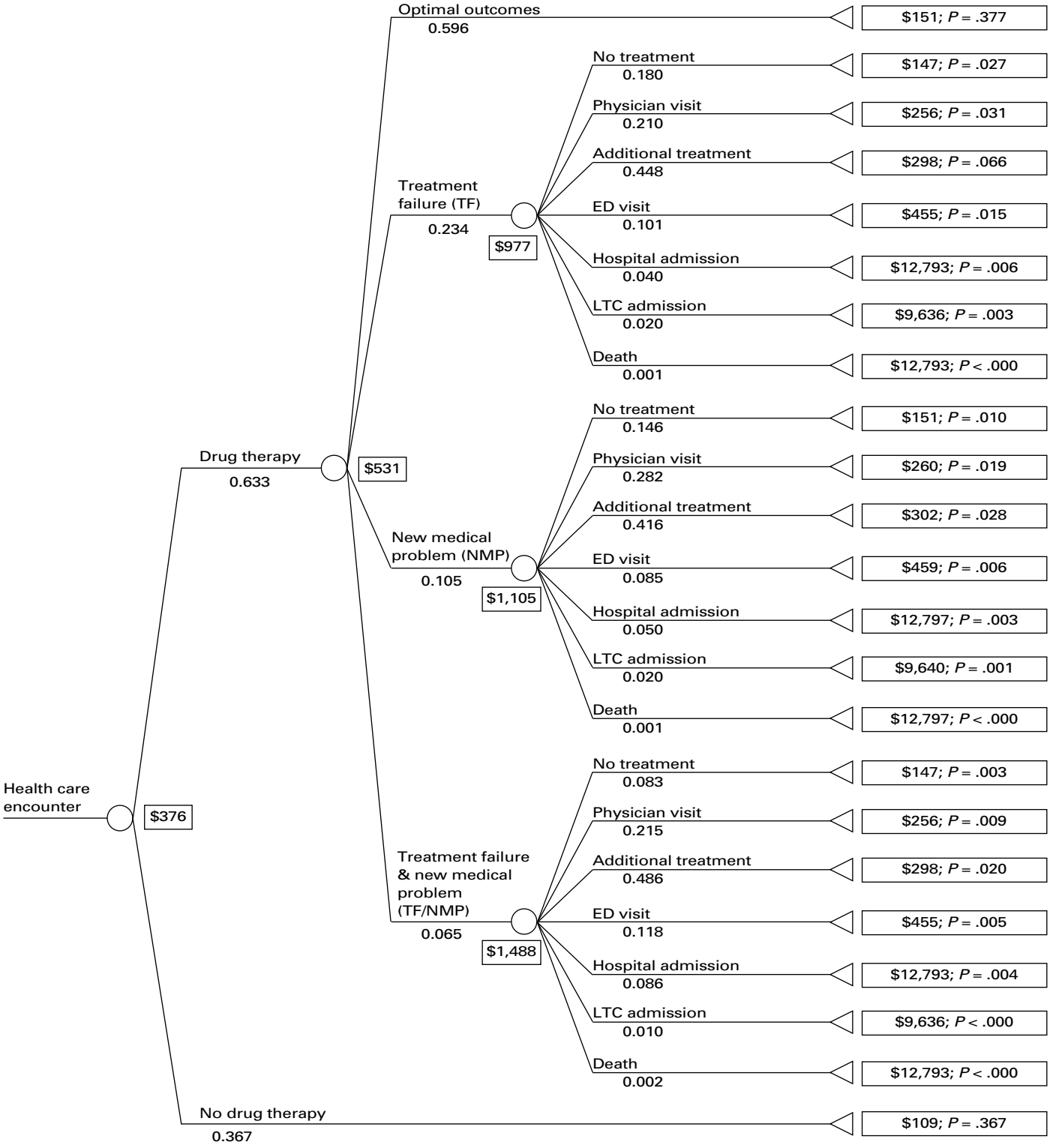
Between July 1999 and March 2000 we searched journal articles published since 1992 using MEDLINE, International Pharmaceutical Abstracts, tertiary health statistic resources, and other search engines and electronic and printed databases available through the Arizona Health Sciences Library. Search terms used in MEDLINE and IPA searches included *drug therapy, adverse effect, morbidity and mortality, drug-related, drug-induced, drug-related problem,* and *compliance*.

Cost Calculations

We determined the average costs of physician visits, prescription medications, ED visits, hospital admissions, and LTC admissions using the most recent data available before March 2000. To minimize potential variation, we relied heavily on the same costing sources used for the 1995 estimates. The cost of a physician visit was determined using a weighted average of the mean physician fees for new and established patients,[34] reported for 1998. The average cost of a prescription was calculated by dividing the sum of reported sales for both generic and brand prescription drugs by the total number of generic and brand prescriptions dispensed in 1999.[35,36] To factor in TF, an adjusted prescription cost was used; when making this calculation we assumed, as Johnson and Bootman did, that 10% of prescriptions are never filled.[1,32]

The cost of hospital admissions was calculated by dividing the reported hospital revenue from inpatient admissions in 1998 by the number of admissions for that year.[37] LTC-per-admission cost was calculated from reported data, as well, using the 1996 monthly average cost per LTC resident,[38] adjusted for the 1996 average length of stay. As in the Johnson and Bootman study, pathway costs involving additional prescriptions reflected the assumption that LTC admission costs followed additional physician visits, and death cost pathways assumed that hospitalization preceded the final outcome. Each component cost was adjusted to year 2000 dollars. Total pathway costs, then, were sums of the updated costs of individual pathway components.

Figure 1. Drug-Related Morbidity and Mortality[a]



ED = emergency department; LTC = long-term-care.
[a]Derivation of average outcome costs is shown in Table 2.

Table 1. Average Annual Costs of Health Care Resources to Manage Drug-Related Problems[a]

Resource	Previous Cost Estimate[b]	Recent Cost Estimate	% Change
Physician visit	$64	$109	+70
New prescription	$25	$42	+68
ED visit	$312	$308	−1
Hospital admission	$5,415	$12,646	+134
LTC facility admission	$4,571	$9,489	+108

ED = emergency department; LTC = long-term-care.
[a]Rounded to the nearest dollar.
[b]As detailed in Reference 1.

Data Analysis

Conditional probabilities, costs, and sensitivities were calculated and analyzed using decision-analysis software (TreeAge DATA v3.5 for Healthcare, student version: TreeAge Software, Inc., Boston, Mass.) and spreadsheet software (Microsoft EXCEL v7.0 : Microsoft Corporation, Redmond, Wash.). Decision-analysis modeling usually involves six steps:

1. Identifying the decision, including the selection of the decision options to be studied.
2. Structuring the decision and its consequences over time.
3. Assessing the probability that each consequence will occur.
4. Determining the value of each outcome, such as in dollars or utilities.
5. Selecting the option with the highest expected outcome value.
6. Determining the robustness of the decision through sensitivity analysis (i.e., variation of the probability and outcome values over a likely range).[39]

We performed each of these steps and examined the assumptions made by Johnson and Bootman[1] by reviewing articles published subsequently. We focused primarily on steps 3 and 4, because the probabilities of certain outcomes and the costs associated with those outcomes were most likely to have changed in the short time period since the earlier study.

To determine the estimated probabilities of each category of outcomes (node probabilities), we employed a "folding back" technique in which we started from the right side of the decision tree (see Figure 1) and worked leftward, or backward in time. We weighted the cost of each possible outcome in a category (see Table 2) by its probability and added the weighted costs to arrive at the costs given at the nodes. To determine the total cost of illness due to DRPs, we multiplied the average cost of each outcome by the total number of occurrences of that event (see Table 3).

Results

In assessing needed updates to the event probabilities previously estimated by Johnson and Bootman's panel of experts, we found no more reliable estimates published since the earlier article. Instead, recent studies[22,24,27] frequently referred to probabilities reported in the Johnson and Bootman model.[1]

Additionally, the DRP categories developed in 1990 by Hepler and Strand[18] and Strand et al.[19] appear to remain the standards despite the time elapsed since their publication. Therefore, we retained Johnson and Bootman's original DRP categories and probabilities for our decision tree.[1]

New data defining costs associated with drug-related morbidity and mortality were readily available, and these formed the basis of new cost calculations. The costs used in the updated model are presented alongside the 1995 estimates in Table 1. The average cost of a prescription was calculated by dividing the sum of reported sales for both generic and brand prescription drugs ($111,101,894,000) by the total number of generic and brand prescriptions dispensed in 1999 (2,712,456,000).[35,36] Adjusted to year 2000 dollars,[33] the average cost of a new prescription was found to be $42. An adjusted prescription cost of $38 was used to calculate TF and TF/NMP costs attributable to the fact that approximately 10% of prescriptions that are never filled. [1,32]

We calculated hospital admission cost by dividing the reported hospital revenue from inpatient admissions in 1998 ($407,650,369,271) by the number of admissions for that year (33,766,000).[37] Adjusting the result to year 2000 dollars gave us an average hospitalization cost of $12,646. LTC-per-admission cost was based on a monthly average of $3,135 per LTC resident,[38] adjusted to the 1996 average length of stay of 83.4 days. Length of stay was determined by dividing the 5,224,710 LTC patient days[37] in 1999 by the year's 62,610 admissions. Hence, this LTC admission was calculated to be $9,489 per stay when adjusted to year 2000 dollars. As in the 1995 study,[1] pathway costs involving additional treatment assumed that LTC admission costs followed additional physician visits, and cost pathways involving death assumed that hospitalization would precede the final outcome.

Folding back the decision tree (Figure 1) with updated terminal node costs revealed that a TF cost an average of $977; an NMP, $1,105; and a combined TF and resulting NMP, $1,488. Furthermore, the average cost of any drug therapy was shown to be $531, and a health care encounter (considered a physician visit) was expected to cost $376. The latter cost figure has no intrinsic value and is simply the weighted mean cost of the entire model (i.e., all possible outcomes), as it was in 1995.[1]

Pathway cost totals were based on a hypothetical cohort of

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

Pathway Outcome	Initial Treatment ($)		Cost of Negative Therapeutic Outcome					Total Pathway Cost
	Physician Visit[32]	Drug[33,34]	Physician Visit	Drug	ED Visit[22]	Hospital Admission[35]	LTC Admission[35,36]	
Optimal outcome	$109	$42	—	—	—	—	—	$151
Treatment failure (TF)[b]								
No treatment	$109	$38[b]	—	—	—	—	—	$147
Physician visit	$109	$38	$109	—	—	—	—	$256
Additional prescription	$109	$38	$109	$42	—	—	—	$298
ED visit	$109	$38	—	—	$308	—	—	$455
Hospital admission	$109	$38	—	—	—	$12,646	—	$12,793
LTC admission	$109	$38	—	—	—	—	$9,489	$9,636
Death	$109	$38	—	—	—	$12,646	—	$12,793
New medical problem (NMP)								
No treatment	$109	$42	—	—	—	—	—	$151
Physician visit	$109	$42	$109	—	—	—	—	$260
Additional prescription	$109	$42	$109	$42	—	—	—	$302
ED visit	$109	$42	—	—	$308	—	—	$459
Hospital admission	$109	$42	—	—	—	$12,646	—	$12,797
LTC admission	$109	$42	—	—	—	—	$9,489	$9,640
Death	$109	$42	—	—	—	$12,646	—	$12,797
TF and NMP[b]								
No treatment	$109	$38	—	—	—	—	—	$147
Physician visit	$109	$38	$109	—	—	—	—	$256
Additional prescription	$109	$38	$109	$42	—	—	—	$298
ED visit	$109	$38	—	—	$308	—	—	$455
Hospital admission	$109	$38	—	—	—	$12,646	—	$12,793
LTC admission	$109	$38	—	—	—	—	$9,489	$9,636
Death	$109	$38	—	—	—	$12,646	—	$12,793
No drug therapy	$109	—	—	—	—	—	—	$109

ED = emergency department; LTC = long-term-care.
[a]Rounded to the nearest dollar.
[b]Estimated drug costs for TF and TF/NMP are reduced by 10% to reflect rate of new prescriptions never filled.

ambulatory care patients making a total of 734,493,000 physician office visits in the United States in 1996, as reported by the Centers for Disease Control and Prevention[40] (compared with the 669,689,000 visits in 1992, as referenced by Johnson and Bootman[1,32]). We estimated the drug-related morbidity and mortality cost-of-illness to be $177.4 billion annually (Table 3), compared with the $76.6 billion arrived at by Johnson and Bootman. Of the updated amount, hospital admissions accounted for $121.5 billion (69%) per year, and LTC admissions represented $32.8 billion (18%). Physician visits accounted for another $13.8 billion (8%), whereas ED visits and additional treatment cost more than $5.8 billion (3%) and $3.5 billion (2%), respectively.

We evaluated the cost of illness for its sensitivity to changes in the component cost estimates (e.g., hospital admission cost) as well as for its sensitivity to pathway probabilities. For the former, an arbitrary 10% was either added to or subtracted from the cost of each component in turn, and then all together. This analysis alone revealed a range in the cost of illness from $159.6 billion to $195.1 billion.

When probability estimates for the most highly probable treatment event, additional treatment (i.e., additional prescription), were similarly varied, the total cost of illness ranged from $174.6 billion to $180.2 billion. Varying these probabilities resulted in little change in the overall expected cost of treatment (range, $373 to $380), but doing so expanded the range of costs associated with physician visits to between $11.8 billion (7%) and $15.9 billion (9%) while affecting none of the other categories.

Discussion

Duplicating the Johnson and Bootman model in detailed spreadsheets ensured that the framework had been accurately replicated, i.e., that using the same outcome probabilities and cost estimates from the 1995 study produced identical results. Additionally, duplicating the Johnson and Bootman decision-analytic model allowed for a high

Table 3. Summary of Cost of Illness—Drug-Related Morbidity and Mortality

	No. of Events	Approximate Cost/Event[a]	Total Cost (%)	% Increase Since 1995
Total physician visits	126,846,567	$109	$13,826,275,829 (7.8)	85.3
Total hospital admissions	9,609,722	$12,646	$121,524,547,854 (68.5)	156.1
Total ED visits	18,703,833	$308	$5,760,780,460 (3.2)	8.3
Total LTC facility admissions	3,454,460	$9,489	$32,779,372,199 (18.5)	127.7
Total additional prescriptions	83,735,556	$42	$3,516,893,339 (2.0)	81.9
Total deaths	218,113	—	—	
Total			$177,407,869,681 (100)	131.7

ED = emergency department; LTC = long-term-care.
[a]Rounded to the nearest dollar.

degree of confidence that confounding factors were not introduced by any structural changes to the tree. Replacing only the outcome-specific cost estimates and resource use values (number of annual physician visits) produced results that were not confounded by calculations performed differently from the 1995 study. Thus, neither modeling nor calculations should have contributed to the differences in cost estimates between the two studies.

The majority of cost increases appeared to result from the estimates of hospital and LTC admission pathway costs, which according to estimates in the literature were more than twice the 1995 estimates (Table 1). The data summarized in Table 3 revealed that the greatest increases in drug-related morbidity and mortality costs were in total hospital admissions (2.6 times), total LTC admissions (2.3 times), and total physician visits (1.9 times). These events contributed the most to the total cost-of-illness estimate of $177.4 billion.

Sensitivity analysis of the cost-of-illness components showed that a 10% variance in hospital admission pathway cost produced the greatest change (7%) in total cost of illness (range, $159.6 billion to $195.1 billion). The same degree of variance in LTC admission pathway cost created a 2% variation in overall cost of illness, whereas the variance in the cost of a physician visit resulted in less than 1% variation in the total cost. Nevertheless, these three component costs contributed the most to variances in the $177.4 billion cost of illness attributable to sensitivity analyses. These same component costs were responsible for the difference between the $76.6 billion figure from 1995 and the $177.4 billion from our study.

Sensitivity analysis was also performed for the event with the highest probability of occurrence within each arm: additional treatment following a DRP. A 10% variance in the probability of "additional treatment" resulted in an average cost of illness ranging from $174.6 billion to $180.2 billion.

The $308 average cost of an ED visit was based on the 1996 study by Dennehy et al.[24] ($283; range, $65 to $501), at the University of California–San Francisco Medical Center, adjusted to year 2000 dollars.[33] As the only cost not derived from the same source[41] referenced earlier by Johnson and Bootman, this estimate was chosen as a slightly more conservative one. All other cost data were based on updated information from the same sources used in the 1995 study. This strategy was used to minimize variation in data sources as a confounding variable in the update. Because the data used in the comparison study spanned approximately 3 years (1991–94) or were standardized to those years, and cost data used here spanned about 4 years (1996–2000), any confounding that might have been introduced by different spans of time should have been minimized. Additionally, this study standardized data to year 2000 dollars, just as the previous study standardized to 1992 dollars.

As Johnson and Bootman did, we assumed that 10% of prescriptions resulting in TF were never presented by patients for filling.[1,32] No definitive data estimating the number of never-filled prescriptions could be found in the literature. However, the adjustment of cost estimates for TF, with or without an NMP, clearly represents a problem in pharmacoeconomics studies. Several studies, including the Lipid Research Clinics–Coronary Primary Prevention Trial (LRC-CPPT) and the Helsinki Heart Study (HHS), remain landmark testaments to the complex issue of adherence because they revealed that different levels of adherence, especially in cases where reported intake misrepresents actual adherence, can lead to unexpected errors in economic analyses of outcomes.[42] Moreover, the 10% rate seemed appropriate based on recent data from Matsui et al.,[43] who documented never-filled rates of 7% for prescriptions for pediatric patients, and Watts et al.,[44] who estimated a 30% never-filled rate among adult patients with asthma.

Because DRPs contribute significantly to health care costs, the 1999 Institute of Medicine (IOM) report[45] focused government and public attention on the issue and reinforced the call to action issued by investigators for the heart trials previously mentioned. In addition, press releases from the American Society of Health-System Pharmacists[46] and other discussions of DRPs and the medication use process are increasingly working their way into the awareness of both the general public and the health professions.[47–50] The opportunity costs (i.e., dollars unavailable for other purposes) resulting from medication-related errors, or DRPs, as the IOM report points out, will be paid by purchasers and patients. The results of this study have the potential, therefore, to help break the cycle of inaction alluded to by the IOM committee.

Limitations

This study had several limitations. First, as in the Johnson and Bootman study, DRPs and related costs were merely estimates and included only ambulatory care settings in the United States, limiting generalizability. However, no decision-analysis model can characterize all of the dimensions of health care that contribute to drug-related morbidity and mortality.[51] Rather, modeling may provide insight into where the process under study may be improved.

The scant data available to update treatment patterns and probabilities of events limited the current analysis to cost data. Sensitivity analysis was used to minimize the effects of using estimates from the original expert panel.

Our statistical analysis was limited in comparison with that performed in 1995. Johnson and Bootman performed analyses using mean values and ranges for resource use estimates determined from the survey responses of their panel of clinical experts. In the current study, sensitivity analysis was limited to (1) assessing a ±10% change in each of the cost components, such as hospital admission cost and ED visit cost, and (2) a ±10% change in "additional treatment" and "no treatment" arms of the model. Nonetheless, estimates from this study relied heavily on data in the literature and on tertiary health statistics summaries, perhaps enhancing the real-world precision of the results.

The data used for modeling and calculations came from published medical literature, and our search strategies may have missed relevant studies. However, we recognized this potentially confounding element from the beginning and made every attempt to discover all data relevant to drug-related morbidity and/or mortality.

Our study did not address several issues studied by Johnson and Bootman, including the impact of pharmaceutical care on the results of modeling analyses, comparisons between the cost of drug-related illness and other sources of morbidity and mortality, or subgroup analyses of populations susceptible to the deleterious effects of drug-related illness. Pharmaceutical care may reduce DRPs, as may other considerations. Additional research into the scope of and solutions for the problem of drug-related morbidity and mortality is needed and should be encouraged.

Conclusion

This study updated Johnson and Bootman's 1995 cost-of-illness model assessing the morbidity and mortality associated with DRPs. Since 1995, the costs associated with DRPs have more than doubled to an estimated annual average of $177.4 billion. Hospital admissions and LTC admissions remain the primary contributors to this total cost. Drug-related morbidity and mortality continue to pose a serious medical and economic problem for society. More attention should be directed toward developing solutions that reduce preventable morbidity, mortality, and costs associated with DRPs.

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MEDICINE TAX STAMPS

Antikamnia

Acetanilid was introduced into medicine as an analgesic in 1886, and 4 years later was incorporated as the main ingredient of a proprietary called *Antikamnia* (meaning "against headache"). The remedy was trademarked September 3, 1890, by the Antikamnia Chemical Company of St. Louis, Missouri. However, in 1894 the firm foolishly added codeine, heroin, quinine, and salol to the product formula to gain more sales. This led Samuel Hopkins Adams, in his famous 1906 series of articles titled "The Great American Fraud," to single out *Antikamnia* as a prime example of the need for the 1906 Federal Food and Drugs Act. Each bottle of *Antikamnia* had to be sealed with one of these 1900-1901 Spanish-American War medicine tax stamps issued by the U.S. government.

George Griffenhagen, Vienna, Virginia

Barry's Tricopherous

New York City wig maker Alexander C. Barry turned his attention to helping people's real hair in 1859, and commenced the manufacture of *Barry's Tricopherous*. The product, which contained castor oil, alkanet root, oil of bergamot, alcohol (and later cantharides), was promoted to "eradicate scruf and dandruff, prevent baldness, and cure diseases of the scalp." Barclay and Company of New York City assumed the manufacturing rights for *Tricopherous* in 1874. Before this, each bottle had to be sealed with one of these Civil War medicine tax stamps.

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