Key concepts:


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In our previous paper (The Need to Assess the Value of Medicines), we pointed out that pharmaceutical agents are the fastest rising expenditure component of the health care system, certainly in the most affluent countries. It was the goal of that paper to highlight the need for comprehensive assessment by health care systems of the value of medicines. Secondly, we attempted to identify obstacles to such assessments and identified potential solutions that could remove these obstacles.

We concluded that the relative contribution of drugs to a population should be assessed stringently by modern clinical and health economic research tools. Furthermore, it was argued that evidence-based data on the value of medicines must inform political and budgetary decisions, so to shift the focus of debate from cost to value. This brings us to the current focus of this paper. It is our first objective to further articulate the medical efficacy versus effectiveness gap that supports the hypothesis that society is not realizing the complete value of medicines. Finally, we will review a variety of solutions that may serve as examples and illustrations of how the “gap in value” can be closed. The conclusion will raise the question as to who will provide leadership to demonstrate the value of medicines.
The simple answer to this question is “no”! As clearly pointed out by Bootman and Langley\textsuperscript{[1,10]}, there is a theoretical and practical gap between the efficacy and effectiveness of drug therapy. Drugs are developed with the goal of proving efficacy and safety. However, this evaluation is conducted under ideal study conditions as required by regulatory agencies. The actual effectiveness and safety of a given medicine as measured in the “real world” is usually inferior to its efficacy estimate. This is portrayed in figure 1. Additionally, not only is there a potential reduction in the overall value equation, there is increased variability, and unpredictability in drug response.\textsuperscript{[2]}

During the mid-sixties, published reports of the Task Force on Prescription Drugs\textsuperscript{[3]} identified the potential strengths and value of pharmaceutical agents. Also identified, were the potential problems and the misuse associated with drug use. Two decades later in 1989, Henri Manasse published a two-part paper in the American Journal of Hospital Pharmacy entitled, “Medication misuse in an imperfect world: drug misadventuring as an issue of public policy”\textsuperscript{[4-5]}. In his treatise, he articulated various problems in the misuse and overuse of medications. Following this was the 1990 paper that is now considered a classic published by Hepler and Strand, which identified the various issues associated with medications as they are utilized within the healthcare setting\textsuperscript{[6]}. As stated by Hepler and Strand, positive clinical outcome is the ultimate goal in the use of medications. Medicines are used to cure disease; reduce or eliminate symptoms; arrest or slow disease; and optimally, to prevent disease or symptoms from occurring and enhance overall quality of life.
Unfortunately, when medications are not used properly, new medical problems occur, or treatment failure exists as a result of specific drug-related problems. Hepler and Strand concluded that a major function of the pharmacy profession should be to enhance the quality of drug therapy, and thus reduce the risk of drug-related morbidity and mortality.

Furthermore, Hepler and Strand\(^5\) identified several causes that result in less than optimal drug therapy, which ultimately lowers the probability of a positive outcome for a given patient. They are listed in Table 1. In an earlier paper, Strand et al\(^6\) classified drug-related problems into eight categories (Table 2). As indicated, each of the eight types of drug-related problems can result in adverse conditions for the patient, thus lowering the overall value of a given medication. In a study in 1998, adverse drug reactions were shown to be a leading cause of mortality in the United States\(^8\).

**Table 1**

<table>
<thead>
<tr>
<th><strong>Factors that contribute to low quality drug therapy</strong>(^6)</th>
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<tbody>
<tr>
<td><strong>1. Inappropriate Prescribing of Drug Therapy</strong></td>
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<tr>
<td>• Inappropriate regimen (drug, dosage form, dose, route, dosage interval, or duration).</td>
</tr>
<tr>
<td><strong>2. Inappropriate Pharmaceutical Delivery</strong></td>
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<tr>
<td>• Drug not available when needed because of: (1) Economic Barriers (e.g., pharmacy does not stock drug, patient will not or cannot purchase it), (2) Biopharmaceutical Barriers (e.g., inappropriate formulation), or (3) Sociological Barriers (e.g., institutional drug distribution system or patient caretaker fails to administer drug).</td>
</tr>
<tr>
<td>• Dispensing Error Involving: (1) Incorrect or inappropriate relabeled prescription, or (2) Incorrect or missing patient information or advise</td>
</tr>
<tr>
<td><strong>3. Inappropriate Behavior by the Patient</strong></td>
</tr>
<tr>
<td>• Compliance with inappropriate regimen</td>
</tr>
<tr>
<td>• Noncompliance with appropriate regimen</td>
</tr>
<tr>
<td><strong>4. Patient Idiosyncrasy</strong></td>
</tr>
<tr>
<td>• Idiosyncratic response to the drug</td>
</tr>
<tr>
<td>• Mistake or accident</td>
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<tr>
<td><strong>5. Inappropriate Monitoring</strong></td>
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<tr>
<td>• Failure to detect and resolve an inappropriate therapeutic decision</td>
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<tr>
<td>• Failure to monitor the effects of a treatment regimen on the patient</td>
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In essence, drug-related morbidity is the phenomenon of therapeutic malfunction or miscarriage, and/or the failure of a therapeutic agent to produce the unattended therapeutic outcome. As defined by Hepler and Strand, a drug-related problem is any event or circumstance involving a patient’s drug treatment that interferes with the achieved or optimal outcome. The concept includes both treatment failure and the creation of new medical problems. Evidence suggests that a large proportion of drug-related morbidity is actually preventable. It can be further suggested that drug-related problems can not only result in poor clinical outcome, but can have a tremendous negative impact on the economics of health care. Unfortunately, there is little research to define the full scope of the problem. Therefore, the extent of drug-related morbidity and mortality should be of great importance to health care practitioners, administrators, patients and society as a whole.

It was in 1995 that Johnson and Bootman began to estimate the “efficacy vs. effectiveness” gap in both clinical and economic terms. Their article published in the Archives of Internal Medicine presented the economic and clinical consequences of drug-related morbidity and mortality occurring in U.S. ambulatory care settings. Their study demonstrated that Drug-related problems accounted for $76.6 billion dollars of additional healthcare expenditures. This was approximately equivalent to the pharmaceutical expenditures during the same time period. This was the first such article attempting to quantify the clinical and economic extent of medication problems.
Figure 2 provides a summary of the incidence of problems associated with drug-related problems, whereas Table 3 provides a summary of the economic impact. Similar conclusions can be made in other countries, namely in Europe. Most recently, Ernst and Grizzle updated the Johnson/Bootman article by utilizing the same methodology with more current figures.

Table 3: 1-Year Economic Outcomes of Drug-Related Morbidity and Mortality in the U.S., 1995

<table>
<thead>
<tr>
<th>Results</th>
<th>Number</th>
<th>Expenditure ($ billions)</th>
</tr>
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<tbody>
<tr>
<td>Hospital Admissions</td>
<td>6.8 Million</td>
<td>47.4</td>
</tr>
<tr>
<td>Long-Term Care Admissions</td>
<td>3.2 Million</td>
<td>14.4</td>
</tr>
<tr>
<td>ER Visits</td>
<td>17.1 Million</td>
<td>5.3</td>
</tr>
<tr>
<td>Deaths</td>
<td>198,000</td>
<td>N/A</td>
</tr>
<tr>
<td>Total Cost</td>
<td></td>
<td>$76.6</td>
</tr>
</tbody>
</table>

N/A: not applicable
They estimated that in 2001, drug-related morbidity and mortality resulted in an additional $177.4 billion dollars of healthcare expenditures. This amount far exceeded the expenditures for the basic cost of medications in 2001. Furthermore, it should be pointed out that both of these studies did not include the suffering and decreased quality of life that numerous patients encounter during sub-optimal and failed therapy so the overall impact was under estimated.

Much of the literature prior to the Johnson /Bootman\(^{10}\) and Ernst/ Grizzle\(^{18}\) articles describing drug-related problems and the economic consequences, focused on hospitalization secondary to adverse drug affects or medication non-compliance and were fairly narrow in scope.

Sullivan et al\(^{19}\) surveyed available literature using the meta-analytic technique, estimated that non-compliance alone accounted for 5.3% of hospitalizations; direct medical costs associated with these hospitalizations were estimated to be 8.5 billion dollars. The authors estimated that an additional 17-25 billion dollars in indirect costs was related to drug therapy non-compliance.

Another study conducted in Canada,\(^{20}\) estimated that the total cost of non-compliance alone, was greater than US$100 billion. This has also been identified as a major issue throughout the world.\(^{21}\) While non-compliance is certain to account for a large proportion of drug misadventuring, limiting the analysis to the issue of non-compliance alone underestimates the true extent of drug-related morbidity and mortality.

The report that attracted clinical, political and media attention, was the Institute of Medicine 1999 report “To Err is Human”.\(^{22}\) This report summarized the critical research to date, and elicited renewed focus from public and professional media to errors in health care, along with an extensive discussion of medication related problems.

Prior to this point, drug-related problems were considered the “Silent Disease in America”\(^{30}\). This report continues to make a call for action to make health care safer for patients. Many similar such studies published in the European press, point to a similar incidence and prevalence of such drug-related problems.\(^{11-13, 31-37}\)

The Institute of Medicine points out correctly that no single remedy offers a comprehensive solution and a combination of activities and responsible participation by diverse constituencies in healthcare is required. An essential first step is that adequate leadership will be necessary for improvement.
In the USA alone,
in 2001, drug-related morbidity and mortality resulted in $177.4 billion dollars of additional healthcare expenditure, which far exceeded the basic cost of medications in that same year.
How can we achieve the full value of medicines?

Another recent report from the Institute of Medicine (IOM) entitled, "Priority Areas for National Action: Transforming Healthcare Quality," called for the development of strategies, goals and action plans for achieving substantial improvement in the quality of care within the next five years. Understanding that resources do not exist to solve every problem, they suggested that selected priority conditions need to be addressed on an immediate basis. In this landmark report, the priority areas for quality improvement included cancer, diabetes, hypertension, ischemic heart disease, depression, and several others. In addition, equally critical was the proper management of medications, including the prevention of medication errors and the overuse of antibiotics. This again points to the building consensus that medication misuse needs to be immediately addressed.

Given the evidence and summaries of such reports, the key question remains, how do we go about improving the overall quality and safety of medication use. In a third landmark report released by the Institute of Medicine in 2001, entitled, "Crossing the Quality Chasm," several key recommendations and strategies were outlined to improve the quality and safety of healthcare in the United States. The report provided guidance and principles for the redesign of healthcare, which would include fundamental changes in the way the system meets the needs of the people it serves. We agree in total with the report. In fact, their proposed strategies for addressing quality in healthcare should serve as a template to improving the quality of the medication use process.
Though the literature is not comprehensive with regard to published reports on the improvement in the medication use process, several key articles have been published during the past decade which provide optimism that medication misuse can be improved and, ideally, prevented. In general terms, many of these studies suggest improvement in the systems approach whereby medications are distributed, prescribed and used. Other publications highlight the changing role of the pharmacist towards improving the overall outcomes from medication usage.

Diverse programs and strategies have been proposed to improve the quality and safety of drug use in ambulatory and institutional settings. These include such systems as computerized monitoring systems to identify and report errors. Systems that utilize bar coding for example, demand that it can minimize errors in the administration of drugs in hospitals. Additionally, standardized decision support systems can be developed to improve drug selection and dosing and monitoring for drug interactions. Also, pharmacy clinics that are directed towards proper monitoring and management of chronic disease have demonstrated great success in the prevention of medication misuse. Diabetic, asthma, cholesterol, and anti-coagulation clinics are excellent examples.

The Institute of Medicine report proposed the following agenda for the redesign of healthcare in the 21st century:

• That all healthcare constituencies, including policymakers, purchasers, regulators, health professionals, healthcare trustees and management, and consumers, commit to a national statement of purpose for the healthcare system as a whole and to a shared agenda of six aims for improvement that can raise the quality of care to unprecedented levels.

• That clinicians and patients, and the healthcare organizations that support care delivery, adopt a new set of principles to guide the redesign of care processes.

• That a set of priority conditions be identified upon which to focus initial efforts, provide resources to stimulate innovation, and initiate the change process.

• That healthcare organizations design and implement more effective organizational support processes to make change in the delivery of care possible.

• That purchasers, regulators, health professions and educational institutions create an environment that fosters and rewards improvement by (1) creating an infrastructure to support evidence-based practice, (2) facilitating the use of information technology, (3) aligning payment incentives, and (4) preparing the workforce to better serve patients in a world of expanding knowledge and rapid change.
Finally elevating the role of the patient and engaging them in strategies and programs that improve compliance and prevention of medication problems with the goal of improving safety has been shown to be extremely successful. As previously mentioned, many such studies have been presented over the past decade, aimed at reducing adverse drug events in hospitals. Particular notice should be given to the study by Leape et al., in which they demonstrated that pharmacists contribute to reducing adverse drug reactions in hospitalized patients. Bates et al. also demonstrated remarkable success. Evans also conducted a study that demonstrated a 70% reduction in adverse drug events as associated with antibiotic usage in intensive care units, which was published in 1998.

Johnson and Bootman published a follow up article which demonstrated that the impact of the pharmacist in ambulatory care settings could reduce the incidence and prevalence of adverse drug events and drug-related problems by as much as 50%, with resulting potential savings in the cost of drug-related morbidity of approximately $45 billion annually. More recently, Gurwitz et al. published their work that demonstrated that pharmacist, in cooperation with physicians and patients, contributed to preventing adverse drug reactions in elderly outpatients.

Bluml et al. demonstrated the value of outpatient “collaborative practice models” between pharmacists and physicians in therapy of hyperlipidemia. When the patient, physician and pharmacist worked as a team, compliance increased by 84% during the first year of treatment, with 46% of those patients reaching their national cholesterol education program treatment goal.

Additionally, Cranor and Christianson identified the positive impact of pharmaceutical care services developed for diabetic patients. This resulted in improved patient satisfaction in regard to the care of their diabetes, and significant cost savings and positive patient outcome in terms of the overall impact of these diabetic management programs. As another illustration of the positive impact of the ambulatory care pharmacists consultation process on patient care, a recent study published in the American Journal of Managed Care by Yuan, Hay, McCombs delineated the overall effect of various models of consultation on patient mortality and hospitalization. They determined that intensive pharmacist consultation targeted at high-risk patients improved survival and decreased hospitalization rates. This was completed over a two-year period and provided compelling evidence that strategies can be employed in ambulatory and institutional settings to improve the overall quality and safety of pharmaceutical drug usage. Again, research published by the World Health Organization and in Europe shows similar results.
CONCLUDING COMMENTS

It is well documented that medication-related problems occur extensively throughout all settings of healthcare.

Additionally, there is increasing evidence of successful strategies to minimize, if not prevent such problems. A key point for discussion is who will provide the necessary leadership to implement such strategies. Some claim\(^{15,39}\) that financial incentives will be essential for any kind of success. Certainly, health professions (e.g. medicine, pharmacy, nursing) need to begin working in collaboration to implement and evaluate interventions aimed at preventing drug-related problems. This will also require attention by payers including both government and large employer groups. It is suggested that directed and strong leadership be taken despite the lack of financial structure, to address this most serious public health issue. Consumer participation will be critical for ultimate success. This has been strongly stated in a most recent article in JAMA in which the authors who studied adverse drug events in the elderly, suggested that partnership between pharmacists, physicians and patients is essential for preventing medication problems.\(^{53}\)

In summary

- There is no need for further investments in investigating and documenting the issue of drug-related morbidity and mortality, in order for action to be taken in this regard by the various stakeholders, and particularly by healthcare professionals;
- There is also enough evidence of strategies to support that action;
- The key to address this problem is the collaboration between the various stakeholders, and particularly between healthcare professionals and patients;
- Further evaluation of the role and responsibility of consumers/patients in this collaborative effort is necessary;
- The current system of incentives to address and curb this problem does not support collaborative efforts in many countries;
- Payers are encouraged to incentivise best practice and collaborative work amongst healthcare professionals;
- In the current vacuum of initiatives in this regard, leadership is essential to implement positive strategies. Pharmacists have a unique opportunity to provide this leadership and avoid professional obsolescence in healthcare.
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