Exploring the Interface Between Medication Safety and Rational Therapeutics:

A Report From the Field

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Delivered at Creighton University on November 5, 2003

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Suggested Citation:
Campbell WH, Galt K. Exploring the Interface Between Medication Safety and Rational Therapeutics: A Report From the Field. The John M. Eisenberg Memorial Lectureship on Therapeutics Research presented at: Creighton University; November 5, 2003; Omaha, NE. Available at: http://www.chainonline.org/home/content_images/Eisenberg_UNCCERT.pdf
Abstract

In the spirit of asking questions that can make a difference, we offer two for discussion. The first, broadly stated, is: Does the separation of medication safety from rational therapeutics into distinct areas of research reflect a useful distinction, or is it a false dichotomy of “good drugs” (the subject of research in therapeutics) and “bad drugs” (the subject of research in medication safety)? Secondly, we ask: Could there be value in defining a drug more abstractly, through a behavioral lens? Doing so would lead to considering provider and patient behavior as another property of a drug, just as important as its dose or absorption.

To bring these questions into focus, we review the various dimensions by which a drug can be defined (e.g., chemical, pharmacologic action, therapeutic benefit) and suggest specific behaviors essential to achieve optimum benefit. Next, we review several drugs that have been withdrawn from the marketplace and ask what provider or patient behaviors would have allowed the drugs (all with proven benefits) to remain available. Recent actions by the U.S. Food and Drug Administration (FDA) to either suggest (e.g., black box warnings) or require (e.g., mandatory risk management plans) facilitating behaviors are offered as validation of this concept. We propose a policy whereby all drug approvals include a “behavioral dimension,” equal in importance and scientific rigor, to the official labeling. Without a clear statement of the requisite behaviors for achieving optimum benefit, no drug monograph can be considered safe and effective. Rather than being a radical departure from current practice, this modest proposal simply synthesizes and projects the trajectory of current policy. In a separate inquiry, we examine a report from researchers at the Creighton University Center for Health Services Research Program (CHRP) in Omaha, Nebraska, who are evaluating the potential of new technologies to improve safety of therapeutics at the point of care. Improving access to drug information is likely to reduce errors in prescribing, and the use of new technologies for standardizing and automating the prescription-writing process can reduce errors even further. To examine these hypotheses, a cohort of 78 physicians in 31 office practices were randomized to receive (or not receive) handheld personal digital assistants (PDAs) loaded with a drug information software package and prescription-printing software. Physicians in the intervention group were trained in the use of the applications and were given the choice to adopt or not adopt them. The findings about the impact of the PDA technology were interesting and useful, but equally important were the findings about the pitfalls of integrating technology with practice.
environments. Practice environments shape our behaviors. So to assure safe and effective use of drugs, we must analyze and design practice environments more carefully, particularly with regard to information technology.
Introduction

In the spirit of asking questions that can make a difference, we propose two. First, does the trend toward separation of medication safety and rational therapeutics into distinct areas of research reflect a useful distinction, or is it a vestige of classifying our pharmacologic agents into a false dichotomy of “good drugs” (the subject of research in therapeutics) and “bad drugs” (the subject of research in medication safety)? Second, is there value in redefining what we consider to be a drug by viewing it more abstractly, that is, through a behavioral lens? Doing so would lead to considering provider behavior to be another property of a drug that is as important—if not more so—as its dose or absorption. To bring both questions to ground level, as John Eisenberg would have wanted, we close with a report from the field that explores where such questions might lead.

Rational Therapeutics and (or?) Medication Safety

Both the public and private sectors have longstanding interests in measuring and improving health care outcomes, and the Agency for Healthcare Research and Quality (AHRQ) has provided national leadership in building a national capacity for conducting research in applied therapeutics. Another growing influence is healthcare purchasers’ desire for comparative research (Drug A vs. Drug B) to manage pharmaceutical benefits. Concern about medication safety gained visibility over the past decade and was elevated to national headlines by the prestigious Institute of Medicine’s attention to the topic.¹ During the same period, AHRQ initiated a major research effort in patient safety and, in a relatively short time span, the Nation had developed an impressive research portfolio characterized by multidisciplinary effort, expanding research support, and important contributions to the professional and scientific literature.

Despite the Nation’s growing interest in maximizing the benefits of drugs, the record of the past 30 years is decidedly mixed with regard to safety. For the period 1971–1993, approximately 2.7% of all new chemical entities approved for market were removed because of safety concerns; the next 2 decades show a withdrawal rate of approximately 2.5% (Fig. 1).² A 1 in 40 product failure rate would be untenable in food, automotive, aerospace, and other critical industries; why, then, should we ask less of the Nation’s pharmacopeia?
We often regard the preceding as a discussion about “unsafe drugs.” However, if from 2.5 to 2.7 percent of drugs can be frankly, if retrospectively, described as unsafe, it does not necessarily follow that the remaining 97% of drugs are safe. The literature is replete with studies on the inappropriate use of medications, projecting thousands of deaths, billions of dollars in costs, and untold pain and suffering attributable to the unsafe use of “safe” medications.3-4

We believe a change in perceptual framework is called for, specifically a change in our vocabulary and taxonomy for describing drugs. Table 1 shows the 10 most recent withdrawals of drugs from the United States market. For purposes of discussion, let us use cerevestatin (Baycol®) as an example. We would typically describe cerevestatin or any other drug in terms of its chemical, pharmacologic, therapeutic, risk, or other properties. We might define cerevestatin as:

A chemical or compound: In the official product labeling of this product, in communications with health professionals, in commercial messages to practitioners, and in many other ways, the initial description of a drug is often as a chemical compound. In the case of cerevestatin, the molecular formula is C_{2}H_{33}FNO_{5}Na, with a conforming structural formula.

A pharmacologic agent: Additionally, we express our understanding of this drug as a pharmacologic agent, specifically a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor that slows cholesterol biosynthesis and reduces cholesterol formation and concentration in hepatic cells.

A therapy or benefit: To move the pharmacologic description from theory to practice, we describe the drug as a therapy or benefit. For example, cerevestatin is an adjunct therapy to diet in the treatment of elevated cholesterol, apolipoprotein B, and triglycerides; it reduces low-density lipoprotein cholesterol and increases high-density lipoprotein cholesterol, although the demonstration of reduction in long-term cardiovascular morbidity and mortality was not completed at the time of market approval.

A risk or safety concern: Adding to the picture, we describe risks associated with the use of the drug. A typical statement for cerevestatin would be that it causes idiosyncratic irreversible rhabdomyolysis with related cardiomyopathy and liver damage, possibly leading to death.

Yet despite these carefully crafted and useful descriptions, the gap between our understanding and use of cerevestatin has resulted in serious public health harm. If we were
required to go one step further and establish explicit provider behaviors as a core description of
the drug, the public health risk would be materially reduced. In official labeling, in drug
monographs, or in textbooks used within a practice setting, the description of a drug would be
considered incomplete without a statement of the practitioner and patient behaviors required to
assure safety and effectiveness of the drug. In the example of cerevestatin, we might further
define it as:

A set of practitioner behaviors:

- Perform and review liver function tests before initiating therapy, at 6–12
  weeks, and then every 6 months.
- Withdraw treatment if alanine transaminase levels are greater than 3 times the
  upper limit of normal (ALT > 3×ULN)
- Monitor patient pharmacotherapy to avoid concurrent use with gemfibrozil.
- Educate patient to monitor and report myalgias; if positive, screen for creatine
  kinase.

A set of patient behaviors:

- Schedule and complete liver function tests at 6–12 weeks initially, then every
  6 months while on therapy.
- Adhere to dosage adjustment schedule based upon results of the liver function
  test, including discontinuation of medication.
- Learn and use essential physical assessment methods for self-monitoring
  adverse effects and act appropriately (e.g., discontinue medication, contact
  physician) when self-monitoring methods indicate action is required.

These explicit behaviors are sometimes implied in package inserts or other labeling (e.g., Dear
Doctor/Pharmacist letters) approved by the FDA. But because these behaviors are developed so
late in the product life cycle, or are so cautiously positioned in the official labeling, they are
more often filed in practitioners’ wastebaskets than in their gray matter.

Adding an explicit statement of the practitioner behaviors required to achieve safe and
effective use of the drug would help everyone focus on clinical applications of the drug. It would
force an integration of our knowledge about the benefits and risks of drugs and increase the
expression of that knowledge in optimum patient care. Not coincidentally, it would require that
we draw upon current research in patient safety and rational therapeutics and recognize common
ground between the two areas of research.

Extending the example of cerevestatin to another drug recently removed from the market (cisapride, Propulsid®), we could envision the following as being:

**Practitioner behaviors:**

- Screen all potential patients before prescribing by using 12-lead electrocardiography. Do not initiate therapy if the corrected QT interval is $>450$ m/sec.
- Review current medication history and avoid initiating therapy in patients with history of cardiac arrhythmia.
- Educate patients to monitor electrolytes and heart rate; discontinue drug if heartbeat becomes irregular.
- Avoid concurrent use with macrolide antibiotics, antifungals, protease inhibitors, phenothiazides, and tricylic antiarrhythmics.

**Patient behaviors:**

- Agree to provide complete history of heart-related syndromes, including records from other practitioners, plus a log of heart rate during work, recreation, rest and at other times.
- Demonstrate skills necessary to for physical assessments related to heart function, including completion of laboratory testing of electrolytes on recommended schedule.
- Maintain current record of all medications used and provide these records to all current health care providers on a regular basis and when requested.

We could continue, using other recently withdrawn drugs, to illustrate the essential behaviors that providers and patients should adopt to ensure safety and effectiveness of high risk-to-benefit drugs. At present, these behaviors are implied but rarely explicit, leading to predictable misunderstanding in the patient-provider relationship. The involvement of behavioral and communication specialists would bring valuable expertise to the development of appropriate vocabulary and taxonomy.

In truth, the addition of a behavioral component to practitioners’ knowledge of drugs is already occurring in a limited form. An expanding number of drugs are being placed on the
market with mandatory risk management plans (RMPs). In some cases, these are drugs the FDA has approved under the fast-track authority granted by Congress to move drugs more quickly to market when there are unique benefits to a population facing serious illness (with limited conventional therapy). In other cases, these are drugs judged by a risk-benefit calculus to require behaviors that adjust both risks and benefits. Table 2 shows a partial list of these drugs.

The RMPs may require (1) prescribers to attest that a patient has a specific diagnosis or does not have a contraindicated condition (e.g., pregnancy), (2) manufacturers to restrict distribution to selected medical or pharmacy practices, and, may require, (3) patients and providers to enroll in registries that monitor patterns of drug use. These and various other tools are, in fact, behavioral dimensions attached to the drugs to adjust risk and benefit toward an optimum balance. The FDA has just released three industry guidances to inform all stakeholders of the circumstances when approved labeling and spontaneous reporting of adverse events are inadequate to achieve an optimum risk-benefit balance. In anticipation of these guidances, most new New Drug Applications are resulting being submitted with an accompanying RMP. The combination of mandatory RMPs by the FDA and voluntary RMPs by industry is a clear example of how provider behaviors are becoming an inseparable element in our definition and understanding of a drug.

The use of another group of drugs could be aided by adding a behavioral dimension to their definition. In contrast to drugs removed from market for safety reasons, these are newly approved drugs that have exceptional promise of benefit. Table 3 shows the list of new chemical entities (NCEs) approved by FDA in 2003 that were designated by the Agency as Category 1, that is, representing a significant therapeutic advantage over existing drugs. These could be considered the “all-star” lineup of drugs for 2003. In each case, the drug represents a new and promising approach to therapy, whether it belongs to a new chemical class (e.g., daptomycin), is a therapeutic agent for a disease previously intractable to drug therapy (e.g., gefitinib), is a new therapeutic target (e.g., enfuvirtide), or other promising breakthrough in therapy. If these drugs come close to achieving our high expectations, we will have added unique and substantial value to our therapeutic armamentarium.

But as we know, success is far from certain. Table 1 showed that the 10 drugs most recently removed from the market have a median life of 2 years, even though some offer significant and unique benefits. Will some of 2003’s all-star drugs be among the group of drugs
removed from market in 2005? If we knew which drugs would face mounting evidence of safety problems, our response would be predictable—we would mandate behaviors that improve the drug’s risk/benefit ratio. Rather than wait for an accumulation of problems, and react to the situation by identifying provider-patient behaviors to correct problems, why not be proactive and identify those behaviors at the outset? Why not identify unique and practical behaviors that can be attached to each drug in order to achieve optimum benefit? The result would be an additional, explicit component of our current practice of describing and using drugs in the U.S. In addition to our current labeling requirements, we would require a clear description of the minimum essential behaviors required of practitioners to make the drug safe and effective in real-world use.

This approach will force all of us—scientists, regulators, and practitioners—to translate our knowledge about drugs into action. As described in the introduction to this paper, it will also require that we identify unique and practical behaviors that can be attached to each drug to achieve optimum benefit. As an interesting sidelight, the FDA’s Guidance Document on Preclinical Risk Assessment recommends that an ideal use scenario be identified for each drug, whereby the use of the drug is “translated into pragmatic, specific and measurable objectives that results in processes or behaviors.” The ideal use scenario is simply another way of expressing the need for a behavioral dimension to our understanding of drugs.

The best historical example of viewing medical science through a behavioral lens might be that of Dr. Rudolf Virchow, the founder of modern pathology. Dr. Virchow, a brilliant Austrian physician/scientist, is best known for postulating that all disease must be understood at a cellular level. Regardless of the presentation of the problem, whether blunt trauma or infectious disease, he argued that we must understand what is happening at the cellular level in order to treat the patient. Had Virchow stopped at this point, he would merely have achieved immortality for founding modern pathology. But Virchow went further, arguing that it is the responsibility of physicians to adopt behaviors that translate cellular understanding of pathology into reduced mortality and morbidity. Virchow stressed that understanding cellular processes must lead physicians to specific behaviors: to educate patients, to eradicate contaminated water, to implement immunization programs in public schools, and, in general, to translate science into behavior. With apologies to Dr. Virchow, we believe his message to us in 2004 would be to understand the chemical, molecular, pharmacologic, and other scientific dimensions of drugs, but
equally important, to express that knowledge in behaviors that move benefits from theory to practice.

The best contemporary example of using a behavioral lens to view products (or services) comes from the world of marketing. Viewing products solely as products can be disastrous: Digital Equipment Corporation sold computers and disappeared, but IBM sold information and thrived; Eastern Airlines sold airline tickets and ended in bankruptcy, but Southwest Airlines sells “bargain destinations” and enjoys record profits; Yahoo sells a search engine and loses market share, but Google™ promises a unique partnership for solving problems and enjoys exponential growth; and so forth. It is only by defining a personal need that can be met through a product, and attaching the requisite behavior, that optimum human value is achieved. So we must also regard drugs as products that can meet a human need, but only if the requisite facilitating behavior takes place. A drug without the requisite behavior from patients or providers is a suboptimal drug.

The University of North Carolina Center for Education and Research on Therapeutics (UNC CERT) has taken steps to bridge the gap between patient safety and rational therapeutic research. As a note of explanation, the UNC CERT has a focus on rational therapeutics for the pediatric population and has a portfolio of 21 active research projects. We have tried to identify synergies between projects that focus on patient safety and others that focus on therapeutic benefits. Similarly, the Creighton University Health Services Research and Patient Safety Center (CHRP) has undertaken research that extends the study of patient safety to include provider behavior, information technology, and systems of care delivery to achieve rational therapeutics. Funding from AHRQ has been instrumental to support this patient safety research and the dissemination of its results. We have come together to illustrate how relationships between patient safety and rational therapeutics can be identified and to describe those relationships. The results come from the Creighton University Computer Prescribing/Order Entry with Drug Informatics Support In Ambulatory Clinics project.8-10

Report From the Field:

One Approach to Integrating the Concepts of Safety With Therapeutics:

Patients and Systems of Care Delivery
Integration of safety and therapeutics is essential for delivering new therapies, improving the design of patient care plans, improving systems of care delivery, and assuring competence of professionals. There are many problems with medication-related safety in the outpatient environment, leading to suboptimal therapeutics and ultimately to risk or harm to patients.\textsuperscript{1,11-15} Although a great deal of research in therapeutics has been conducted in the outpatient environment, there has been little study of patient safety, medication use systems, and the relationship of these two to optimal therapeutics. Current research questions at Creighton University focus on the safety of medication use in the outpatient primary care office. We chose the primary care office practice for study because most primary patient care occurs here, most prescribing takes place in the ambulatory care office practice environment, and the greatest proportion of medication errors are attributed to the prescribing step in the medication use process.\textsuperscript{16}

Some strategies can be expected to improve medication safety in outpatient care, based upon evidence published about inpatient medication use systems.\textsuperscript{17} First, we may be able to improve immediate access to drug information and pharmaceutical decision support through new technologies at the point of patient care, thus likely improving the safety of therapeutics at the point of prescribing. We may further improve the therapeutic value of medications by standardizing and automating the prescription-writing process by using those technologies. Such an approach is likely to reduce problems such as illegibility and omissions of critical information from the face of prescriptions.\textsuperscript{18,19}

Our study was designed to ask the question: “If we introduce these technologies in the primary care office, can we have an impact on prescribing errors?” The research was designed as a randomized, controlled trial of 78 physicians in 31 office practices.\textsuperscript{19} These office practices are representative of the settings where most outpatient health care takes place in the U.S. Fully 85% of the practitioners are family practice physicians, and about one-third are women, with an average age of 42 years. A handheld personal digital assistant (PDA), a drug information software package (Lexi-comp\textsuperscript{®}), and software capable of printing a prescription to a local infrared-ready printer, were provided to the intervention group. This group received training until all demonstrated competence in the use of the hardware and the software applications. The group was then instructed to incorporate use into daily practice; however, this was not a requirement for completion of the study. The study documented the natural adaptation and adoption behavior
of the practitioners toward the PDA and its applications. Pre- and postintervention measurements of prescribing errors were the primary outcomes measures of the intervention.

As we went into the field to introduce the intervention to the primary care offices, we realized there was much more to learn about the environment of care delivery in primary care. To disseminate our results, we needed to understand the current practice environment and its relationship to therapeutic safety: What is the medication safety environment of the outpatient office? How ready are these offices and practitioners to use this technology? What kind of access to drug information decision support is presently in place?

Our premise was that we were introducing an intervention that would have a positive impact. We broadened our work to look at the office structure and to determine what effect this intervention has on the professionals and the system that supports their delivery of care to patients. Baseline information was collected on the access to and quality of drug information resources, readiness of the office technology, and the readiness of the user for technology at point of care.

**Drug Information Resources**

*Access to information resources.* Access to drug information resources is important to therapeutic decisionmaking at the prescribing step. There was a minimal selection by type and number of drug information resources available in print format in the offices, but these resources were not standardized by form or function. A few offices had computer-based drug information sources available on a desktop computer. Accessibility at the point of care was poor, with almost every site keeping the drug information resources in a distant room or location, remote from where clinical decisionmaking took place. Many of the practitioners indicated that they kept information resources in their personal offices away from patient examination rooms. The location of information resources seemed to be based upon the principle that information was something to be “looked up later when I have time,” rather than a real-time resource designed to support clinical decisions. Here is a representative response from one physician:

Where do we keep our drug information sources? We have a computer down the hall on the right, just past the third examination room, around the hallway from the chart storage
area, just behind the patient check in. Are we using them? Well, they are hard to get to quickly….”

**Quality of information sources.** As we improve therapy and safety, we must ask if the quality of the information resources is adequate to support safe prescribing. We conducted an evaluation of the three most widely disseminated handheld drug information resources (Micromedex®, ePocrates®, and Lexi-Comp®) to determine the most adequate drug information resource to include as part of the intervention. Three physicians piloted the intervention PDA, each using all three resources to answer questions relevant to safe prescribing in the primary care setting. Each resource was evaluated and categorized as either: (1) adequate information to answer the question, (2) helpful information but not sufficient for the complete answer, or (3) insufficient information. An inter- and intrarater comparison of references was performed, and Lexi-Comp® emerged as the best choice for this study. As information systems increase in accessibility, the quality of information will continue to be a critical component to supply therapeutic safety and improved quality of care.

**Technology Readiness**

How prepared is the office practice environment for this technology? Our environmental evaluation of the 31 primary care offices revealed these offices are far less ready for a technology-based framework than one might imagine.

*Computerization of the office staff area.* A technology-ready office will have computer services that provide convenient access to the Internet and practice applications at the point of care. All offices studied had networked computers, most commonly used for exchanging e-mail, word processing, literature searches, and billing or online transactions. Other uses included maintaining patient appointments, tracking employee schedules, maintaining electronic databases, and preparing graphics and presentations. Computers were used by office staff to periodically conduct literature searches on critical questions of practice. However, this function was performed infrequently and was rarely integrated into the daily workflow of the clinic staff.

In our evaluation of office readiness, we found at least 10 different Internet service providers, and 5 versions of office operating systems. Lack of standardized information
technologies makes the use of computer applications more difficult in a multiuser environment. One half of the offices used the Microsoft Windows 95® operating system, which does not support any PDA technology device that requires real-time synchronization of functions such as information backup and search. This meant that one-half of our study sites could not support the intervention we designed, forcing us to change the way we provided the intervention technology to our practitioners; that is, we provided off-site “hotsyncing” services through the study period.

*Computerization of patient examination rooms.* Many of the practitioners believed their offices were technology-ready. Several of the clinics were wired with cable and had data jacks in the walls of the examination rooms. One physician had worked with an architect to design the exam rooms to support technology and gave us a tour to show us where the data jacks were located—there were no data jacks! What is most revealing about this anecdote is that no computers were ever placed in the examination rooms, so the practitioners did not discover that the data jacks were missing until we asked. We also surveyed sites to determine infrared printing capability and found that most were inadequate. Revealingly, we found that 25 percent of our respondents did not know what “infrared enabled” meant. This circumstance forced a change in our plans to integrate the intervention into existing office printing systems.

*Workflow.* When a technology is incorporated into a routine work function, there is an opportunity to introduce both efficiency (the intended consequence) and inefficiency (the unintended consequence). The technology will only introduce efficiencies if it incorporates user and environmental needs. We defined the broad outlines of the technology intervention; the practitioners decided how the technology would be integrated within their practices (e.g., location, changes in workflow). The goal was to create the most efficient process possible within the unique aspects of each practitioner’s office environment. Generating prescriptions by using infrared printing devices is a clear example of new technology that must be integrated into the workflow. Prescriptions are printed every 10 to 12 minutes throughout the workday for patients seen by practitioners in this environment. Stepping out of the standard workflow to print and retrieve these documents for patients would rapidly lead to delays in the rest of the office. This would not be acceptable to practitioners. We modified the intervention by providing an infrared-enabled printer to each participating practitioner.

The spatial arrangements of the medical offices are not generally designed to support incorporation of new technologies. Examination rooms are typically small, with extremely
limited counter space. Often there is no physical location for installing and storing a printing device or computer. Additionally, practitioners generally move from room to room. Although PDA technology offers the advantage of moving with the practitioner, a printer does not. Therefore, a printer in each room was a commonly expressed need of practitioners, but given the office design and space limitations, it would be difficult for many of the offices to accommodate more hardware in patient examination rooms. Most offices, even those purportedly designed to support technology-based interventions, are found to be problematic when the specific technology requirements are known. Reevaluation of office design, workflow, and the required investment must be conducted to move office practices toward technology readiness.

**Office Medication Safety Survey**

Initial observations of the office environment suggested deficiencies with regard to safety of medications. To study this in greater depth, a 154-item written survey was developed to assess the domain of medication safety in primary care office practice. Items were derived from published evidence as well as reports and standards from private and public organizations. Safety domains were identified by reviewing the areas of safety emphasis from the Institute of Medicine report “To Err is Human: Building a Safer Health System,” the Agency for Healthcare Quality Research patient safety agenda and portfolio, and the scientific literature. Survey items integrated structure, process, and outcome quality concepts relevant to medication safety. All offices participated in the survey.

All of the results of this survey are published elsewhere, however a few key findings are highlighted for this discussion. Nearly half of the offices (44%) had no procedure to respond to a serious medication error. Only 6 percent of the offices labeled samples for patients to assure proper use, and 56 percent reported no procedure for giving prescription samples to patients. One-third of the offices updated the patient’s chart when they renewed orders by phone, suggesting that two-thirds did not update and have inaccurate records of current medications and renewals. And 24 percent of the offices reported having dismissed someone from employment for medication error. The interface between office practitioners and pharmacists also needs to be improved: only 36 percent of the offices reported that when telephoning prescriptions to the pharmacist, the pharmacist repeats back the order.
Prescribing Outcomes

*Adoption of PDA-printed prescribing.* Some preliminary results about the impact of the intervention on prescribing are available. The intervention product was field tested and refined in the study setting, optimizing it for use in the study. We found that the intervention group generated 43 percent of a possible 100 percent of prescriptions electronically. When practitioners were given a choice, some ingrained behaviors surfaced, explaining the 57% of prescriptions still generated by traditional handwritten means. The human factors aspect of technology was critical to the practitioner’s willingness and interest in adapting to and adopting this technology for generating the prescription. Almost all practitioners reported using the PDA to look up drug information. Access to information held high value to prescribers.10

*Legibility of prescriptions.* The legibility problem, which many people think will disappear when electronic prescribing is in place, showed amazing survivability.9 Legibility was studied for 34,645 prescriptions generated by the intervention group. Illegible prescriptions were defined as any order that generated a question about the interpretation of what was written because the handwriting was unclear. After the intervention was introduced, “legible” orders increased from 91 percent at baseline to 95 percent. The remaining 5 percent of illegible prescriptions were all identified in the handwritten group. Illegible orders can only be eliminated when the system technology is able to accommodate all orders and handwritten orders are no longer an option to compensate for system limitations. The handwritten prescription will still be necessary in less-than-perfect systems, and most systems will be less-than-perfect for the foreseeable future.

*Clarity of prescription instructions.* The intervention software included preloaded instructions for patients to be printed on the prescription, such as “do not take with food,” “avoid alcohol,” “take at bedtime,” and so forth. Upon evaluation, the rating of vagueness of instructions actually increased for the PDA intervention group. We believe the reason for this increase is the individual approach each prescriber used in writing instructions. Prescribers would use the PDA until they had to enter their own message in handwritten text. As a result, there were more clear, unique prescriptions in the handwritten group than in the PDA group. This means that the application was actually counterproductive in not accommodating the human
factors needs of prescribers. Technologies must be human-factor compatible; otherwise, even the simplest and most desirable features of technology may not necessarily lead to improvement.

**Inclusion of indication on the prescription.** The prescribing software included a list of indications the prescriber could include on the face of the prescription as an option. There is value to the patient if the indication is included, because accurate counseling by the pharmacist can take place and the patient can avoid confusion concerning concurrent therapies. Pharmacists can educate patients more effectively, complementing the behavioral side of optimizing therapeutics for the patient. Including the indication pull-down menu resulted in the indication for treatment on the prescription going from 11 percent prior to intervention to 35 percent post-intervention. The 3-fold increase in a desirable prescribing behavior demonstrated the remarkable ability of technology to improve practice when the workflow process, technology, and prescriber support are aligned.

A previously published study illustrates the importance of the professional’s role in integrating knowledge of therapeutics and safety. In this small demonstration study, pharmacists had an independent research team study the process of receiving and filling prescriptions to determine the number and type of errors that were made. The team allowed errors to progress to the point of the pharmacist’s final check and counseling. In their work, 89 percent of the errors committed in the preparation and dispensing process were caught at the time of patient counseling. The integration of this knowledge by the professional—with the intention of caring properly for the patient—is essential to achieving safe care. This integration is also necessary to continue to ask some of the best research questions, such as: What more evidence do we need about the value of counseling for protecting the patients from harm?

**Implications and Lessons Learned**

Separation of the study of therapeutics from the study of safety will diminish our ability to draw inferences across domains. The combined knowledge of these two areas should be studied holistically, in the context of patient care. Our research experience in ambulatory office practices reinforces the importance of studying the interrelationships among interventions intended to improve safety, and the professionals, systems, and patient outcomes. Our national philosophy should be to combine and integrate the expertise of patient safety with rational
therapeutics; to do so, we must identify explicit provider behaviors that are essential to effective and safe drug use. This approach will force all of us—scientists, regulators, and practitioners—to translate our knowledge about drugs into beneficial action.

If we are to achieve practitioner (and patient) behaviors that support safe and effective drug therapy, we must pay attention to the constraining and enabling factors in the practice environment. Administrative directives may be an attractive option for some, but are doomed to failure if the environment fails to support, or even acts to prevent, the desired behaviors. A healthy skepticism about the planned capabilities of practice environments, versus the actual performances of those environments, is recommended in implementing new technologies to improve patient safety and optimum pharmacotherapy.

References


TABLE 1. — *Ten drugs most recently withdrawn for safety or effectiveness concerns in the United States*

<table>
<thead>
<tr>
<th>Drug (generic)</th>
<th>Date withdrawn</th>
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<tbody>
<tr>
<td>Baycol (cerevastatin)</td>
<td>August 2001</td>
</tr>
<tr>
<td>Raplon (rapacuronium)</td>
<td>April 2001</td>
</tr>
<tr>
<td>Lotronex (alosetron)†</td>
<td>November 2000</td>
</tr>
<tr>
<td>Propulsid (cisapride)</td>
<td>July 2000</td>
</tr>
<tr>
<td>Rezulin (troglitazone)</td>
<td>March 2000</td>
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<tr>
<td>Hismanal (astemizol)</td>
<td>July 1999</td>
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<tr>
<td>Raxar (grapafloxin)</td>
<td>February 1999</td>
</tr>
<tr>
<td>Duract (bromphenac)</td>
<td>June 1998</td>
</tr>
<tr>
<td>Posicor (mibefradil)</td>
<td>June 1998</td>
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<tr>
<td>Seldane (terfendadine)</td>
<td>January 1997</td>
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*Median time on the market for these drugs was 2 years.

†Returned to market in 2001.
TABLE 2. — *Examples of drugs* with risk management plans

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<tbody>
<tr>
<td>bosentin</td>
</tr>
<tr>
<td>clozapine</td>
</tr>
<tr>
<td>dofetl ideology</td>
</tr>
<tr>
<td>fentanyl citrate</td>
</tr>
<tr>
<td>isotretinoin</td>
</tr>
<tr>
<td>mefreprestondesoidum oxybate</td>
</tr>
<tr>
<td>thalidomide</td>
</tr>
<tr>
<td>trovafloxacin mesylate</td>
</tr>
<tr>
<td>alosetron</td>
</tr>
</tbody>
</table>

*Many of these drugs are multi-source products and are listed by generic name.*
TABLE 3. — Approved new chemical entities rated “1” for significant therapeutic advantage in 2003

<table>
<thead>
<tr>
<th>New chemical entity</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fuzeon (enfuvirtide)</td>
<td>HIV/AIDS</td>
</tr>
<tr>
<td>Samavert (pegvisomant)</td>
<td>Acromegaly</td>
</tr>
<tr>
<td>Emend (aprepitant)</td>
<td>Antiemetic</td>
</tr>
<tr>
<td>Iressa (gefitinib)</td>
<td>Non-small-cell lung cancer</td>
</tr>
<tr>
<td>Velcade (bortezomib)</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>Retataz (atazanavir)</td>
<td>HIV/AIDS</td>
</tr>
<tr>
<td>Cubicin (daptomycin)</td>
<td>Methicillin-resistant <em>Staphylococcus aureus</em></td>
</tr>
</tbody>
</table>
### Table 4. — Access to drug information resources

<table>
<thead>
<tr>
<th>Clinics in region with resources</th>
<th>Top 10 drug information sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>Physicians Desk Reference (PDR)</td>
</tr>
<tr>
<td>16</td>
<td>Sanford Guide to Antimicrobial Therapy</td>
</tr>
<tr>
<td>15</td>
<td>Harriet Lane Handbook</td>
</tr>
<tr>
<td>11</td>
<td>Monthly Prescribing Record (MPR)</td>
</tr>
<tr>
<td>10</td>
<td>The Red Book</td>
</tr>
<tr>
<td>10</td>
<td>The Washington Manual of Medical Therapeutics</td>
</tr>
<tr>
<td>8</td>
<td>The Medical Letter</td>
</tr>
<tr>
<td>7</td>
<td>Merck Index</td>
</tr>
<tr>
<td>5</td>
<td>Drugs in Pregnancy and Lactation</td>
</tr>
<tr>
<td>5</td>
<td>PDR Monthly</td>
</tr>
</tbody>
</table>
### TABLE 5. — *Optimal drug information source for medication safety*

**Intrarater Comparison of References — Medication Safety Evaluation**

<table>
<thead>
<tr>
<th>Rater</th>
<th>Micromedex® Average Score</th>
<th>ePocrates® Average Score</th>
<th>Lexi-Drugs® Average Score</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rater 1</td>
<td>2.1</td>
<td>2.0</td>
<td>2.4</td>
<td>p = .07</td>
</tr>
<tr>
<td>Rater 2</td>
<td>2.1</td>
<td>2.0</td>
<td>2.6</td>
<td>p &lt; .05</td>
</tr>
<tr>
<td>Rater 3</td>
<td>1.9</td>
<td>2.0</td>
<td>2.6</td>
<td>p &lt; .05</td>
</tr>
</tbody>
</table>

**Interrater Comparison of Each Reference — Medication Safety Evaluation**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Rater 1</th>
<th>Rater 2</th>
<th>Rater 2</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micromedex®</td>
<td>2.1</td>
<td>2.1</td>
<td>1.9</td>
<td>p = 0.49</td>
</tr>
<tr>
<td>ePocrates®</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
<td>p = 0.99</td>
</tr>
<tr>
<td>Lexi-Drugs®</td>
<td>2.4</td>
<td>2.6</td>
<td>2.6</td>
<td>p = 0.32</td>
</tr>
</tbody>
</table>
Figure 1. New chemical entities (NCEs) withdrawn for safety or efficacy reasons, 1971–2003. Data source: US Food and Drug Administration. *New chemical entities withdrawn for safety or efficacy reasons as of October 1, 2003.

Data source: US Food and Drug Administration. *New chemical entities withdrawn for safety or efficacy reasons as of October 1, 2003.

Extrapolation to children of safety and efficacy data generated for adults requires careful attention to potentially important differences between these two populations. The safety of drugs, for instance, needs to be supported by appropriate research with the targeted age group. Some medications that are completely safe for adults may produce toxic effects in children. Hospital pharmacists reported ongoing difficulties in attempting to obtain a medication history on admission. Both parties agreed that the introduction of standard protocols and a designated seamless care pharmacist would improve medication safety at the interface. Most communication occurred between the community pharmacy and hospital on a Friday and also after 3 pm in the evening. When communication did occur the issue was resolved in 81% of all cases. Medication that required a follow up prescription from a patient’s family doctor following a hospital visit was incorrectly transcribed by th