Recommendations for Generating, Evaluating, and Implementing Drug-Drug Interaction Evidence

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In October 2009, a 2-day, multistakeholder, national conference was held in Rockville, Maryland, to discuss and propose methods to improve the drug-drug interaction (DDI) evidence base and its evaluation and integration into clinical decision support (CDS) systems. The conference featured participants representing consumers, health care providers, those responsible for relevant policies and guidelines, and developers and vendors of DDI compendia, databases, and CDS systems. One desired outcome of the conference was to prepare recommendations on critical issues surrounding DDI evidence. A set of recommendations was developed to improve the generation, evaluation, and translation of DDI evidence into CDS systems based on presentations by experts and the supporting literature. These recommendations were reviewed initially by conference moderators, speakers, and Scientific Steering and Planning Committee members, and subsequently by all attendees. The following recommendations were developed to increase patient safety by improving the relevance and assessment of DDI evidence: conduct well-designed studies to determine the incidence, outcomes, and patient-level risk factors for DDIs; use a systematic and transparent process for evaluating the DDI evidence in order to estimate the severity and risks of DDIs; and improve the integration of DDI evidence into electronic CDS. Opportunities exist to improve the DDI evidence base, develop and promote a systematic approach for evaluating the evidence, and integrate this evidence into meaningful CDS.

Key Words: drug information, drug interaction, drug safety, patient safety, clinical decision support, literature evaluation, evidence-based medicine, adverse drug reaction.

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to DDIs were addressed. The conference was funded by a grant from the U.S. Department of Human Services Agency for Healthcare Research and Quality (AHRQ) along with support from relevant industry sponsors to help cover the meeting costs. The issues related to DDIs intersect many segments of health care; thus, participants representing a broad range of constituents were invited to the meeting. A total of 73 stakeholders attended the program, including individuals representing the U.S. Food and Drug Administration (FDA), AHRQ, drug information and compendia providers, health plans, health care institutions, pharmacy associations, academia, and consumers. Detailed information about the program has been published previously. The focus of this report is to present the three recommendations that resulted from conference discussions and supporting literature.

Background

A drug interaction is defined as an alteration in a clinically meaningful way of the effect of a drug (object drug) as a result of coadministration of another drug (precipitant drug). Although some DDIs may be used for therapeutic benefit, this article focuses on those with detrimental clinical consequences. Drug-drug interactions may be pharmacokinetic (i.e., the delivery of the object drug to its site of action is altered by the precipitant drug) or pharmacodynamic (i.e., the response of the object drug is modified by the precipitant drug without changes in drug concentrations) in nature. A potential DDI (PDDI) occurs when two drugs known to interact are coprescribed for a patient, regardless of whether harm ensues.

The prevalence of PDDIs reported in the literature is variable, primarily due to the variety of study methods used. Using pharmacy claims from two large health plans, one study estimated PDDI frequency ranging from 6.2–6.7% of all prescriptions. A survey of a nationally representative sample of 3005 community-residing older adults reported that 4% of the individuals were at risk of a “major” DDI, with half of these from over-the-counter drugs. Despite efforts to minimize exposure to hazardous drug combinations, the evidence indicates that hundreds of millions of PDDIs may occur annually. The frequency of PDDI-associated harm is unknown but it is likely to be quite small. Yet, when DDIs occur, the consequences can be life-threatening and, in some cases, fatal. Although many adverse reactions are unavoidable, harm caused by known DDIs is frequently preventable.

Systematic failures are largely to blame for exposure to DDIs. Problems include limitations in knowledge, interpretation, and application of DDI evidence, as well as poor-quality data. The current literature suggests that prescriber knowledge of DDIs is lacking. Results from a national survey of prescribers found that less than half (43%) of the potentially interacting drug pairs were correctly identified. In addition, other studies have found that the ability of pharmacists to identify PDDIs is relatively poor. Furthermore, the reliability of DDI information sources used by both prescribers and pharmacists is problematic. Several reports have documented inconsistencies in DDI information provided by compendia, in product labeling, and in DDI alerts in electronic prescribing or pharmacy information systems. Attention to DDI alerts by prescribers and pharmacists is also problematic. Decision support aids are not a replacement for sound clinical judgment, yet these resources are preferred over relying on one’s memory to detect PDDIs and determine the clinical relevance for a particular patient. However, many deficits in the consistency, timeliness, sensitivity, and specificity of available DDI information sources and decision support still exist.

Recommendations

A set of recommendations for generating, evaluating, and implementing DDI evidence was
developed through an iterative process. The authors drafted initial recommendations and provided them to conference moderators, speakers, and Scientific Steering and Planning Committee members for review and comment. Although these recommendations do not represent a consensus statement, all participants had the opportunity to provide feedback. The following recommendations, developed as actionable steps, were considered by the primary authors to be the most relevant to enhance patient safety.

Recommendation 1: Conduct Well-Designed Studies to Determine the Incidence, Outcomes, and Patient-Level Risk Factors for Drug-Drug Interactions

Action Items

1. The International Society for Pharmacoepidemiology, the American Society for Clinical Pharmacology and Therapeutics, and other professional societies must highlight the need for population-based DDI research.
2. The National Institutes of Health and AHRQ need to support prospective clinical trials and pharmacoepidemiologic research on DDIs.
3. The FDA should encourage the pharmaceutical industry to conduct prospective phase IV clinical trials and other postmarketing studies to identify possible patient-level risk factors for potential DDIs.

Discussion

The evidence for most DDIs is weak or severely limited in generalizability, and the real-world consequences of drug interactions are essentially unknown. Yet, this information is important for clinicians to make reasonable risk-benefit estimates for patients and to guide therapeutic decision making. Further postmarketing research, especially population-based studies, is needed to assess the incidence, outcomes, and patient-level risk factors for DDIs.

The DDI evidence base consists of case reports, retrospective analyses, extrapolations from in vitro data, and few well-controlled studies. For example, a systematic overview of the warfarin interaction literature rated the majority of the evidence (82% [148/181]), which primarily consisted of case reports (88% [130/148]), as poor quality. Of the fair-to-good quality studies (18% [33/181]), 85% (28/33) included healthy individuals who characteristically are not representative of the population typically exposed to PDDIs. Furthermore, the quantity of evidence supporting the absence of DDIs is even less than that supporting their existence. Such information could help identify noninteracting alternatives to drug combinations that should be avoided.

Case reports may provide the first evidence of DDIs; however, using these reports as the sole source has several disadvantages. They are often poorly described, leading to speculation and inaccurate statements about causal relationships. This is especially problematic when erroneous conclusions are drawn from these reports and included in product labeling. For example, many case reports involving warfarin and antibiotics suggested that an interaction existed. However, two population-based analyses found that when the infection was controlled for, only the antimicrobials that inhibit cytochrome P450 (CYP) 2C9 metabolism showed a significant interaction.

Premarketing DDI studies commonly evaluate surrogate end points in healthy subjects. Therefore, some premarketing DDI predictions use data that may not correlate with the complexities of patient populations such as those with chronic diseases, the elderly, women, or children. When a new product is marketed, it is difficult to apply available DDI evidence to clinical practice. Premarketing data should serve only as a starting point for more comprehensive postmarketing research using appropriate sample size, duration of therapy, commonly coadministered drugs, and relevant comorbidities or high-risk populations. Pertinent clinical end points should also be evaluated, taking into account mitigating and extending factors that govern the risk of DDIs.

Electronic data systems created by payers and government agencies that include millions of patients provide an opportunity to investigate the clinical relevance of interactions, including the ability to identify relatively rare outcomes. Administrative data may have limitations, including gaps in eligibility or turnover, failure to capture self-paid and nonprescription drugs, inability to determine severity of preexisting disease, and confounding by indication; however, recognition and thoughtful research design mitigate these challenges.

Making determinations about clinically significant interactions requires quality studies that
evaluate basic pharmacology and drug elimination as well as epidemiology and outcomes. Data from real-world drug use should take precedence because meaningful evidence to inform clinical decisions requires quantification of risk in customary practice. The lack of information on epidemiology, risk, and relevance of PDDIs in clinical practice may lead to overestimation or underestimation of adverse clinical outcomes and failure to account for patient-specific risk factors. It is essential that DDIs are evaluated in the population of patients for whom the drug is intended, underscoring the need for additional postmarketing and population-based studies to assess the true effects of disease states and other patient-specific factors on the clinical consequences of DDIs.

Recommendation 2: Use a Systematic and Transparent Process for Evaluating the Drug-Drug Interaction Evidence in Order to Estimate the Severity and Risks of Drug-Drug Interactions

Action Items

1. Stakeholders need to collaborate to establish standards for DDI evidence evaluation criteria for consistent use by tertiary drug reference and knowledge base vendors. Key stakeholders may include developers and vendors of DDI compendia and databases, health care providers, academia, and government agencies.

2. Researchers and other stakeholders need to validate existing or newly developed instruments for appraising the quality of individual DDI studies and the overall strength of evidence for a particular DDI.

3. Stakeholders—such as editors, developers, and end users of CDS software and compendia—should require consistent application of transparent and systematic methods to assess DDI evidence.

4. Purchasers and end users of DDI information should take responsibility for understanding DDI evidence evaluation criteria and the editorial processes used to categorize the risk of a DDI.

Discussion

There is considerable discordance among drug knowledge sources concerning the drug interactions of greatest importance. Studies that evaluate DDI information in prescription product labeling compared with other sources also report inconsistencies. Reasons for the variation may include differing definitions of terminology, methods used to evaluate causality, approaches to evidence appraisal, and severity rating systems. However, when DDI information sources are evaluated or compared, it is important to distinguish between referential sources (e.g., compendia) and knowledge bases used for CDS systems (e.g., DDI alerts). A referential source of information typically is more complete (e.g., listing theoretical DDIs), whereas a database used for CDS is more limited to DDIs that require provider action (e.g., education, monitoring, or change in therapy). Yet another challenge with DDI information sources is that the evaluation and categorization methods used by compendia editors and knowledge base vendors are frequently unclear to the end user. Therefore, it is vital that a transparent, systematic approach to evaluating DDI evidence, risk, and relevance is adopted.

The FDA has taken steps to improve the quality and usefulness of DDI information in product labeling. These steps include the following: providing study guidance to sponsors of new drug and biologic license applications, implementing a new format for prescription drug information with specific improvements in how DDIs are described, and indexing certain categories of information in a structured product labeling format to allow rapid searching and sorting of relevant product information within CDS and e-prescribing systems. Despite this, problems still exist regarding the clinical usefulness of DDI information in product labeling. Another concern is that some compendia and knowledge base vendors may include DDIs listed in official product labeling for medical-legal reasons. Because of liability concerns, drug knowledge base vendors may have a legal incentive to include almost all possible interactions. This approach undermines identification of truly clinically significant DDIs in practice because of a large number of false positives that arise when the databases are adopted “off-the-shelf” to drive CDS, without appropriate customization or filtering. Using a systematic evidence-based approach to evaluate DDI data and the resulting severity classification may provide a legal basis for minimizing liability when agents are shown to have a low probability of clinically significant interactions in the literature.
Appraisal of DDI evidence may occur at two levels: the quality of an individual study, and the overall strength of evidence for an interaction. It is essential to first critique individual study quality to prevent drawing erroneous conclusions for the entire body of evidence for a specific DDI. However, no single assessment tool is applicable across all study designs, and most of the available evaluation methods are intended for prospective trials, an uncommon study design in the DDI literature.

Published guidelines for submitting a drug-related case report for adverse events are available. The International Society for Pharmacoepidemiology and the International Society of Pharmacovigilance support these guidelines that provide general statements about requisite or highly desirable elements and patient-level factors (e.g., disease severity, concomitant therapies, dosing and administration) that are needed to establish the validity of association of an adverse event. However, the authors acknowledged that some elements are not relevant for reports involving DDIs. The Naranjo adverse drug reaction probability scale is a 10-item instrument that uses previous evidence and patient-level data (i.e., case report) to assess the likelihood that an adverse event is drug related. Despite its many relevant questions related to DDIs, this instrument fails to specifically address more than one agent given concurrently, a necessary condition for DDIs. To address the limitations of the Naranjo scale, the Drug Interaction Probability Scale (DIPS) was developed. This 10-item instrument assesses causality for case reports and takes into consideration previous credible reports, consistency with known interactive properties, time course of the interaction, results of dechallenge and rechallenge, and alternative explanations (Table 1).

The DIPS tool seems appropriate for evaluating DDI case reports, although formal evaluation of its validity and reliability has not been published. However, it has good face validity and appears to provide a much-needed tool for authors, editors, and reviewers to assess DDI case reports.

When publishing a recommendation about the risk-benefit attributes of a DDI, it is necessary to summarize the quality of evidence across multiple studies. Evaluation of the body of evidence for medical treatments commonly involves hierarchical rating schemes such as those used in evidence-based medicine. However, a unique approach is needed to evaluate DDI evidence. Some DDIs do not require randomized controlled trials to confirm their existence. With advances in the understanding of drug interaction mechanisms, it is possible to predict many PDDIs based on the interactive properties of the drugs. Using the pharmacodynamic and pharmacokinetic properties of a drug as a basis for these interactive properties may allow one to intelligently predict interactions without placing

Table 1. Drug Interaction Probability Scale

<table>
<thead>
<tr>
<th>Question</th>
<th>Score</th>
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<tr>
<td>1. Are there previous credible reports in humans?</td>
<td>+1</td>
</tr>
<tr>
<td>2. Is the interaction consistent with known interactive properties of the precipitant drug?</td>
<td>+1</td>
</tr>
<tr>
<td>3. Is the interaction consistent with known interactive properties of the object drug?</td>
<td>+1</td>
</tr>
<tr>
<td>4. Is the event consistent with the known or reasonable time course of the interaction (onset and/or offset)?</td>
<td>+1</td>
</tr>
<tr>
<td>5. Did the interaction remit upon dechallenge of the precipitant drug with no change in the object drug? (if no dechallenge, use “unknown” or NA and skip Question 6)</td>
<td>+1</td>
</tr>
<tr>
<td>6. Did the interaction reappear when the precipitant drug was readministered with continued use of object drug?</td>
<td>+2</td>
</tr>
<tr>
<td>7. Are there reasonable alternative causes?</td>
<td>-1</td>
</tr>
<tr>
<td>8. Was the object drug detected in the blood or other fluids in concentrations consistent with the interaction?</td>
<td>+1</td>
</tr>
<tr>
<td>9. Was the drug interaction confirmed by objective evidence consistent with the effects on the object drug (other than from Question 8)?</td>
<td>+1</td>
</tr>
<tr>
<td>10. Was the interaction greater when the precipitant drug dose was increased or less when the precipitant drug dose was decreased?</td>
<td>+1</td>
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NA = not applicable.

Total scores indicate the following likelihood of a drug-drug interaction: > 8 = highly probable; 5–8 = probable; 2–4 = possible; < 2 = doubtful.

Consider clinical conditions, other interacting drugs, lack of adherence, risk factor. A “no” answer assumes that enough information was presented so that one would expect any alternative causes to be mentioned. When in doubt, answer “unknown” or “NA.”
patients unnecessarily at harm. In contrast, conducting prospective clinical trials to assess harm induced by certain DDIs is unethical. In addition, observational studies may constitute a more useful research design to assess DDI-related harm because the drugs are used in the context of normal prescribing and drug-taking behaviors. Once a DDI is predicted based on its interactive properties, evidence from real-world use is vital to confirm the association with adverse clinical outcomes and to evaluate the magnitude of harm and relevant risk factors.

Few published methods are available for evaluating DDI evidence. One such system was used for developing a DDI database in Swedish and Finnish computerized CDS systems (Swedish, Finnish Interaction X-referencing [SFINX] database). The classification categories for clinical relevance (A–D) and level of documentation (0–4) were derived from an earlier Swedish DDI classification system (Table 2). A “0” level of documentation was introduced to categorize potentially dangerous interactions that have not been, and probably never will be, documented in clinical studies. Another approach described in the literature was a systematic assessment of DDIs for CDS systems in the Netherlands. The following four core parameters were used to assess each DDI: evidence supporting the interaction; clinical relevance of the potential adverse reaction; risk factors identifying patient, drug, or disease characteristics; and incidence of the adverse reaction. A 5-category scale ranging from 0–4 was used to assess the quality of the evidence for a DDI, with 4 being the highest quality (Table 3). For interactions for which substantial evidence was lacking but predicted to be relevant based on interactive qualities, detailed information on the mechanisms of the interaction was required to deem it relevant. This structured DDI assessment method merits consideration for more widespread use, although further validation of this approach is needed.

A systematic approach for evaluating DDI evidence must include patient- and drug-related factors that may exacerbate or ameliorate an interaction. For example, patient factors may include age, concomitant therapies, and impairment of physiologic functioning such as renal or hepatic disease, and genotype or phenotype. Drug-related factors may include dose, sequence of administration, and route of administration. Authors and editors are strongly encouraged to account for patient- and drug-related factors when evaluating the evidence for the purpose of classifying DDI severity. Furthermore, clinicians must consider these factors as part of the management strategy before exposing a patient to a known interaction.

Recommendation 3: Improve the Integration of Drug-Drug Interaction Evidence into Electronic Clinical Decision Support

**Action Items**

1. The AHRQ and the Office of the National Coordinator for Health Information Technology (ONC) should support research on the optimum approach to integrate DDI information into CDS systems for end users to prevent patient harm while simultaneously improving efficiency and reducing nuisance alerts.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Definition</th>
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<tr>
<td><strong>Clinical relevance</strong></td>
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<tr>
<td>A</td>
<td>Minor interaction of no clinical relevance</td>
</tr>
<tr>
<td>B</td>
<td>Clinical outcome of the interaction is uncertain and/or may vary</td>
</tr>
<tr>
<td>C</td>
<td>Clinically relevant interaction that can be handled (e.g., by dosage adjustments)</td>
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<tr>
<td>D</td>
<td>Clinically relevant interaction; the combination is best avoided</td>
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<tr>
<th>Documentation</th>
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<tbody>
<tr>
<td>0</td>
<td>Data derived from extrapolation on the basis of studies with similar drugs</td>
</tr>
<tr>
<td>1</td>
<td>Data derived from incomplete case reports and/or in vitro studies</td>
</tr>
<tr>
<td>2</td>
<td>Data derived from well-documented case reports</td>
</tr>
<tr>
<td>3</td>
<td>Data derived from studies among healthy volunteers and/or pilot studies among patients</td>
</tr>
<tr>
<td>4</td>
<td>Data derived from controlled studies in relevant patient populations</td>
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<tr>
<th>Scale</th>
<th>Category of Evidence</th>
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<tr>
<td>0</td>
<td>Pharmacodynamic animal studies: in vitro studies with a limited predictive value for the human in vivo situation; data on file</td>
</tr>
<tr>
<td>1</td>
<td>Incomplete, published case reports (no rechallenge or dechallenge, presence of other factors to explain the adverse reaction)</td>
</tr>
<tr>
<td>2</td>
<td>Well-documented, published case reports; retrospective analyses of case series</td>
</tr>
<tr>
<td>3</td>
<td>Controlled, published interaction studies in patients or healthy volunteers with surrogate end points</td>
</tr>
<tr>
<td>4</td>
<td>Controlled, published interaction studies in patients or healthy volunteers with clinically relevant end points</td>
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</table>
2. Stakeholders should collaborate to produce evidence-based CDS for DDIs and coordinate with the ONC initiatives on meaningful use criteria. Stakeholders may include the AHRQ, FDA, Centers for Medicare and Medicaid Services (CMS), health care professional associations, quality organizations (e.g., Pharmacy Quality Alliance), health care providers, health care systems, academia, and developers and vendors of DDI compendia and knowledge bases.

3. The AHRQ, ONC, or a collaboration of stakeholders should create mechanisms to share evidence-based DDI knowledge and best practices. For example, they could explore the feasibility of a national data repository or knowledge clearinghouse for collecting high-quality, evidence-based DDI information for public sharing.

4. The AHRQ, ONC, or a collaboration of stakeholders should develop and promote a national data standard for integrating DDI evidence into meaningful CDS.

5. Stakeholders need to participate in a series of meetings aimed at improving translation of DDI evidence into meaningful CDS. Stakeholders may include health care providers, those responsible for relevant policy and guidelines, and developers and vendors of DDI compendia, databases, and CDS systems.

6. Purchasers and end users of DDI decision support need to understand the capabilities and limitations of their CDS systems.

7. Purchasers and end users should seek CDS software that permits customization to promote patient safety within their unique health care systems.

Discussion

Incorporating DDI alerts as a means of CDS for e-prescribing and other clinical information systems is commonplace and encouraged by the ONC. Unfortunately, implementation of this technology has resulted in a high proportion of alerts that are either ignored or insufficiently evaluated by end users. Enhancing the utility of this important clinical tool is crucial to improving patient safety.

The full potential of DDI CDS is hindered by a large number of false positives for nonexistent or clinically irrelevant interactions and a lack of well-designed user interfaces. Furthermore, end users receive DDI alerts as part of a series of drug safety warnings (e.g., drug allergy, duplicate therapy, inappropriate dose), which may also affect perception of alerts. Numerous studies document high rates of “overridden” DDI alerts and extensive discontent with alerts perceived as inappropriate, insignificant, disruptive, or unnecessary. Therefore, it is imperative for DDI screening software developers and vendors to design systems that provide useful alerts and/or allow for local customization to meet the needs of end users.

Currently, any safety benefits derived from DDI alerts likely result from a small proportion of all alerts presented to clinicians. In addition, fewer more specific alerts may increase clinicians’ perceived benefits of DDI warnings. An expert panel estimated that DDI alerts presented to ambulatory care prescribers in Massachusetts likely prevented 402 adverse drug events in 2006 including death, permanent disability, and temporary disability. The estimated cost savings were $402,619. Of interest, a mere 10% of DDI alerts were responsible for 60% of adverse events and 78% of the cost savings.

Despite some of its limitations, important work has been done to improve DDI decision support. For example, a preliminary mechanism-based DDI knowledge base was developed to provide more accurate and useful information to clinicians rather than current approaches that simply tabulate and index pairwise interactions of drugs. Several studies have also reported strategies for increased acceptance rates based on stratifying alerts by severity levels and interrupting for only the most serious warnings. A reduction in the number of critical PDDIs was observed in an outpatient setting after implementing a program that combined an active pharmacist intervention with inclusion of only the most severe alerts. Use of expert opinion may also help reduce the volume of DDI alerts of minimal clinical value. For example, ambulatory care providers were more likely to accept DDI alerts that were independently judged as being of high clinical value by an expert panel. The ONC funded the Advancing CDS project to develop a consensus-based list of DDIs and assess how malpractice risk may impede optimal use of CDS.

In addition to evaluating methods to safely and effectively improve the “signal-to-noise” ratio (i.e., ratio of alerts with highest clinical value to alerts with minimum clinical value), further research is warranted to assess DDI alert content, format, and presentation to end users.
A high-quality knowledge base is useful only in the presence of a well-designed CDS system and user interface.\textsuperscript{48} For example, filters can be created to decrease the total number of alerts triggered. Customization of alerting logic to accommodate local preferences and practice patterns is also possible.\textsuperscript{49, 50} A simulation study of prescribers’ handling of drug safety alerts found that enhanced training for end users combined with more concise warnings and increased alert specificity would be beneficial.\textsuperscript{51}

Internal methods to categorize and determine the relevance of DDIs for CDS have been developed by various experts and organizations, although a gold standard does not exist. A validated approach and process for sharing best practices are needed. The idea of a national data repository or knowledge clearinghouse for collecting high-quality, evidence-based drug information for public sharing with vendors and local organizations has been proposed.\textsuperscript{20, 48, 52} A repository may provide an additional benefit of alleviating some of the liability issues that prompt commercial vendors to include clinically irrelevant DDI alerts in their systems. However, more research is needed to define tolerable sensitivity and specificity levels for DDI alerts under different circumstances.\textsuperscript{53}

Beyond creating a mechanism to improve and share DDI knowledge, a valuable step is to work toward a national data standard for integrating DDI evidence into CDS. Standardized components might include the following: drug names; a standard set of interaction descriptions, including mechanisms; strength of evidence, including citations for the interaction; clinical outcomes associated with the interaction; incidence of adverse outcomes; management strategies (e.g., recommended actions to take such as options for noninteracting alternatives and/or monitoring); patient-level risk factors (e.g., sex, age, comorbidity, disease severity); and other risk or mitigating factors (e.g., dose, timing, sequence of administration).\textsuperscript{25, 40} It is unclear whether a scale for DDI severity is necessary because the manageability of the interaction is a component of the risk. Therefore, a structured assessment system that accounts for management options and specific modulation factors may be more practical.\textsuperscript{54} Such a classification system may help differentiate between drug combinations that require specific management strategies and those to avoid in most or all situations.\textsuperscript{25, 54} By using a standard set of descriptors for DDIs, implementation of CDS may be more precisely customized for local preferences and different end users.\textsuperscript{48}

In addition to system issues described earlier, efforts to educate end users (clinicians) are imperative.\textsuperscript{51, 55} Users of computerized DDI CDS (and those who make purchasing decisions) must understand and explore the options available within their given system to optimize use of these tools without compromising patient care.

Conclusion

A set of recommendations was developed as a result of a multistakeholder DDI conference on how to better integrate the evidence into health information technologies. These recommendations focus on three distinct but related issues that must be addressed to improve patient safety. Significant opportunities exist for improving the evidence base for DDIs, developing and promoting a standard systematic approach to evaluating DDI evidence, and integrating this evidence into meaningful CDS. Although this conference created a forum for presentation and discussion of the issues, much work is needed at all levels. In particular, additional research is needed to validate methods for assessing the quality of evidence for DDIs and to investigate the most appropriate methods for integrating warnings about possible harm to ultimately improve end-user knowledge. Furthermore, identification of patient risk factors that contribute to or diminish patient harm in the presence of DDIs is needed. Eliminating the harm induced by DDIs will require directed and sustained efforts by all facets of the health care delivery system.

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References


