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Consensus Recommendations for Systematic Evaluation of Drug-Drug Interaction Evidence for Clinical Decision Support

Richard T. Scheife¹, Lisa E. Hines², Richard D. Boyce³, Sophie P. Chung⁴, Jeremiah Momper⁵, Christine D. Sommer⁶, Darrell R. Abernethy⁷, John Horn⁸, Stephen J. Sklar⁹, Samantha K. Wong¹⁰, Gretchen Jones⁴, Mary Brown², Amy J. Grizzle², Susan Comes⁴, Tricia Lee Wilkins¹¹, Clarissa Borst¹², Michael A. Wittie¹¹, Alissa Rich¹³, and Daniel C. Malone²

¹Tufts University School of Medicine, Boston, MA, USA

²University of Arizona College of Pharmacy, Tucson, AZ, USA

³University of Pittsburgh Department of Biomedical Informatics, Pittsburgh, PA, USA

⁴Epocrates, San Mateo, CA

⁵University of California, San Diego, Skaggs School of Pharmacy and Pharmaceutical Sciences, La Jolla, CA, USA

⁶First Databank, Inc., South San Francisco, CA, USA

⁷Office of Clinical Pharmacology, U.S. Food and Drug Administration, Office of, Silver Springs, MD, USA

⁸University of Washington School of Pharmacy, Seattle, WA, USA

⁹Wolters Kluwer Health, Indianapolis, IN, USA

¹⁰Cerner Multum, Denver, CO, USA

¹¹U.S. Office of the National Coordinator for Health Information Technology, Washington, DC, USA

¹²Elsevier Clinical Solutions, Tampa, FL, USA

¹³formerly Cancer Treatment Centers of America, Boca Raton, FL, USA

Abstract

Background—Healthcare organizations, compendia, and drug knowledgebase vendors use varying methods to evaluate and synthesize evidence on drug-drug interactions (DDIs). This situation has a negative effect on electronic prescribing and medication information systems that warn clinicians of potentially harmful medication combinations.

Objective—To provide recommendations for systematic evaluation of evidence from the scientific literature, drug product labeling, and regulatory documents with respect to DDIs for clinical decision support.

Methods—A conference series was conducted to develop a structured process to improve the quality of DDI alerting systems. Three expert workgroups were assembled to address the goals of the conference. The Evidence Workgroup consisted of 15 individuals with expertise in pharmacology, drug information, biomedical informatics, and clinical decision support. Workgroup members met via webinar from January 2013 to February 2014. Two in-person meetings were conducted in May and September 2013 to reach consensus on recommendations.

Results—We developed expert-consensus answers to three key questions: 1) What is the best approach to evaluate DDI evidence?; 2) What evidence is required for a DDI to be applicable to an entire class of drugs?; and 3) How should a structured evaluation process be vetted and validated?

Conclusion—Evidence-based decision support for DDIs requires consistent application of transparent and systematic methods to evaluate the evidence. Drug information systems that implement these recommendations should be able to provide higher quality information about DDIs in drug compendia and clinical decision support tools.

1 Background

Exposure to potential drug-drug interactions (DDIs) is a significant source of preventable drug-related harm that requires proper management to avoid medical errors [1]. Studies indicate DDIs harm 1.9 to 5 million inpatients per year and cause 2,600 to 220,000 emergency department visits per year [2–4].

The importance of DDIs as a risk factor for patient harm led the Centers for Medicare and Medicaid Services (CMS) to include DDI clinical decision support (CDS) alerts in the agency's guidelines for achieving meaningful use of electronic health records (i.e., CMS Meaningful Use Core Measure 2) [5]. However, evidence indicates that DDI decision support systems have not successfully reduced exposure to DDIs [6–8]. In the United States, most alerting systems rely on clinical content created, maintained, and sold by knowledgebase vendors [9]. Each organization implements their own approach to classifying DDIs with limited agreement between systems [10–12]. Additionally, CDS systems often alert for DDIs that have limited clinical relevance, which may increase alert fatigue [13] and lead to inappropriate responses [14–16].

In spite of a desire among providers of DDI decision support tools to provide clinically relevant content, improving the state-of-the-art poses several challenges. High quality evidence to support the existence of many DDIs is lacking, there are few controlled clinical studies conducted in relevant populations [17–19], and individual case reports are underreported and often lack information [20]. Compendia and knowledgebase editors use differing approaches to identify and evaluate evidence [10–12]. There are no guidelines or standards for determining clinical relevance of interactions via consistent systematic evaluation or classification [9, 21]. Without such guidance, DDIs may also be inappropriately extrapolated to other drugs within the same therapeutic or pharmacologic class [22]. In an effort to reduce legal liability, system vendors might have an incentive to

include almost all possible DDIs, including those that confer extremely low risk to exposed patients [9, 23].

We conducted a conference series to develop specific recommendations to improve the quality of CDS alerts for DDIs. These activities were supported in part by a conference grant from the Agency for Healthcare Research and Quality (AHRQ) and donations from health information technology (IT) vendors. Use of funds was at the sole discretion of the University of Arizona and according to Department of Health and Human Services requirements. This paper describes recommendations by the Evidence Workgroup to develop and maintain a standard set of DDIs for CDS alerts.

2 Methods

Fifteen individuals with expertise in DDIs, clinical pharmacology, drug information, evidence evaluation, biomedical informatics, and health IT were invited to participate as workgroup panelists. Members represented diverse backgrounds such as academia; journal, compendia, and knowledgebase editors; healthcare organizations; US Food and Drug Administration (FDA); and the US Office of the National Coordinator for Health IT (ONC). We met via webinar from January 2013 to February 2014, with live meetings held in Washington DC (May 2013) and Phoenix, Arizona (September 2013). To ensure that we addressed the most pressing issues we first conducted a search of the literature for papers describing methods for evaluating DDI evidence. From these articles the following questions were then developed by the conference organizers and then reviewed and agreed upon by consensus of the members: (1) What is the best approach to evaluate DDI evidence? (2) What evidence is required for a DDI to be applicable to an entire class of drugs? (3) How should a structured evaluation process be vetted and validated?

Workgroup members were provided access to articles that were deemed relevant for consideration. Experts also identified relevant studies and these were obtained for workgroup members. Each key question was evaluated in light of the available evidence and the collective experience of the workgroup members. Responses to each key question were written and then modified to improve clarity or address issues or concerns. Workgroup recommendations were posted on a project Internet site and feedback was sought from other stakeholders via dissemination to professional societies and organizations.

3 Results

A summary of our recommendations when evaluating the DDI evidence is shown in Table 1. Details about these recommendations are described more fully below.

3.1 Terminology

We recommend consistent use of relevant terminology for evaluation of DDI evidence. In the process of answering the Key Questions, we identified several terms requiring clarification. A complete list of definitions agreed upon by the workgroup is provided in Appendix A, with some key terms described below.

A *DDI* is defined a clinically meaningful alteration in the exposure and/or response to a drug (object drug) that *has occurred* as a result of the co-administration of another drug (precipitant drug) [24, 25]. Response can refer to either precipitating an adverse event or altering the therapeutic effect of the object drug. A *potential DDI* is defined as the co-prescription of two drugs known to interact, and therefore a *DDI could occur* in the exposed patient [25]. Although the distinction between a *DDI* and a *potential DDI* is important, we refer to both as *DDI* throughout this paper for simplicity. A *clinically relevant DDI* is defined as one associated with either toxicity or loss of efficacy that warrants the attention of healthcare professionals. We recommend use of the term *seriousness*, rather than *severity*, to describe the extent to which a *DDI* can or does cause harm [26].

We developed a working definition for narrow therapeutic index (NTI) because many clinically relevant *DDIs* involve drugs with a *NTI*. Similar terms include narrow therapeutic ratio and narrow therapeutic range (NTR). We considered existing *NTI/NTR* definitions (See Appendix B) inadequate for guiding the evaluation of *DDIs* [27]. Although the FDA is developing a definition and list of *NTI* drugs in the context of bioequivalence, these guidelines/definitions would generally be stricter than is needed for managing *DDIs* in clinical practice. Therefore, we define *NTI* drugs as those for which even a small change in drug exposure may lead to toxicity or loss of efficacy. Several scenarios describe what may constitute a “small” change in drug levels: 1) <100% (<2-fold) increase in area under the concentration-time curve (AUC) for the object drug may lead to serious adverse events; or <50% decrease in AUC for the object drug may result in a loss of efficacy with serious therapeutic consequences (e.g., failure of contraception, or virologic failure due to subtherapeutic drug levels).

3.2 Key Question 1: What is the Best Approach to Evaluate DDI Evidence?

Figure 1 illustrates a conceptual model for evaluating *DDIs* to guide clinical decision making. The first step relates to establishing sufficient evidence that a *DDI* exists, followed by questions of clinical relevance and how to present *DDI* recommendations to health professionals. We primarily focused on identifying the best approach to evaluate that a *DDI* exists, with additional consideration for how to establish clinical relevance.

When publishing a recommendation about the risk of a *DDI*, it is essential first to assess the quality of individual studies to prevent drawing erroneous conclusions about the entire body of evidence. Evaluation of medical treatments commonly involves hierarchical rating schemes such as those used in evidence-based medicine. However, a unique approach is needed to summarize a body of *DDI* evidence, which often consists of case reports, retrospective reviews, and extrapolation from *in vitro* studies, with few controlled clinical studies conducted in relevant populations [17, 19, 28]. Some *DDIs* do not require randomized controlled trials to confirm their existence. It is possible to reasonably extrapolate many interactions based on pharmacokinetic (PK) and/or pharmacodynamic (PD) properties of a drug without placing patients at unnecessary or unethical risk. High-quality observational studies and evidence from real-world use can be applied to confirm the association with adverse clinical outcomes and to evaluate the magnitude of harm and

relevant risk factors. Therefore, evidence supporting a DDI may be derived from what would be regarded as less rigorous study designs for other research questions.

3.2.1 Existing DDI Evidence Evaluation Methods—We conducted a search for published methods for evaluating DDI case reports using Medline and also queried panel members for relevant studies. Only one instrument, the Drug Interaction Probability Scale (DIPS) [20], was found to be specifically developed to evaluate individual case reports for DDIs. This 10-item scale was designed to assess an adverse event for causality by a DDI. DIPS was developed to address the limitations of previous assessment instruments, such as the Naranjo scale [29], that failed to evaluate causality associated with concomitant medications. DIPS takes into consideration previous credible reports, consistency with known interactive properties, time course of the interaction, results of de-challenge and re-challenge, and alternative explanations. DIPS also meets published criteria for assessing causality in terms of guiding users to conduct an explicit, transparent, complete, and balanced assessment of the attributes important to causality assessment of whether an adverse drug interaction occurred and exists [30]. A more complete discussion of available instruments is available in Appendix C.

We also searched for published literature of methods that evaluate a collection of evidence relevant to establishing that a DDI exists (see Appendix C) and found two systematic approaches [31, 32]. The first is the approach for developing a DDI knowledgebase in Swedish and Finnish computerized CDS systems (SFINX) [31]. This system categorizes level of documentation (0–4) and clinical relevance (A–D). A “0” level of documentation reflects potentially dangerous interactions that have not been, and probably never will be, documented in clinical studies. The second approach described in the literature is a systematic assessment of DDIs for CDS systems in the Netherlands [32]. Four core parameters are used to assess each DDI: evidence supporting the interaction; clinical relevance of the potential adverse reaction; risk factors related to patient, drug, or disease characteristics; and incidence of the adverse reaction. A 5-item scale is used to assess the quality of evidence for a DDI. The approach requires the existence of a reasonable mechanistic explanation in order to establish a DDI based solely on PK or PD properties.

While the DIPS approach to case report evaluation was considered acceptable, we considered the existing methods for evaluating a body of evidence more complex than necessary because they combine DDI evidence assessment with questions of clinical relevance. Additionally, existing methods do not explicitly address reasonable extrapolation of DDIs from *in vitro* findings, nor do they explicitly address study quality and interpretation in the context of DDIs.

3.2.2 The Need for a New DDI Evidence Evaluation Instrument—Given the limitations of the available tools, we agreed that a new assessment instrument was needed to objectively evaluate a body of evidence to establish the existence of a DDI. It was further agreed that this instrument should include concepts from previously published DDI evidence rating instruments [31, 32] but with fewer categories based on the presence or absence of specific, clearly defined, types of evidence.

Specific guidance is needed for reasonably extrapolating DDIs that are unlikely to be evaluated in clinical trials. Reasonable extrapolation refers to using the knowledge of the mechanism of a DDI to predict the risk of a DDI from one pair of drugs to multiple pairs with similar pharmacologic properties. Extrapolation of PD interactions is commonplace. For example, not every possible combination of a benzodiazepine and ethanol has been studied. Yet, all benzodiazepines are assumed to interact in a similar manner with ethanol. DDIs based on PK mechanisms present more of a challenge to extrapolation because numerous elimination pathways may be involved and it is difficult to predict the magnitude of the interaction without additional data.

Based on the needs described above for a new method to establish the existence of a DDI, we developed the DRUG Interaction Evidence Evaluation (DRIVE) Instrument. The rationale behind the DRIVE Instrument is to: (1) use simple evidence categories; (2) include causality assessment with DDI case reports (via DIPS); (3) apply reasonable extrapolation, including from *in vitro* studies; and (4) address evidence/statements provided in product labeling; and (5) describe study quality criteria and interpretation in the context of DDIs. Systematic evidence review should include a thorough search for relevant published and unpublished literature and, therefore, we also recognized that future work should seek to develop systematic methods for conducting literature searches for assembling DDI evidence [33–37].

FDA documents, such as product labeling, preapproval reviews and post-marketing analyses are essential sources when evaluating DDI evidence [38]. In our collective experience and opinion, the majority of pre-marketing DDI studies conducted and described in product labeling are well designed and executed. However, we agree that DDI content in drug information systems does not always need to align with product labeling, even when that information is listed as a contraindication or boxed warning. This opinion is based upon examples in which the labeling is not consistent with existing evidence [39] and significant variation occurs in the DDIs listed in product labeling compared with published information [34, 35, 40–42]. We acknowledge that the purpose and guidance of labeling is unique, and also that FDA has taken important steps to improve the quality and usefulness of DDI information in product labeling [43–45]. We recommend continued effort to improve the consistency and timeliness of DDI information in product labeling, particularly for older nonproprietary drugs.

3.2.3 Assessing Clinical Relevance—If there is sufficient evidence that a DDI *might* require clinical management, further evaluation is needed to establish the clinical relevance. Clinical outcomes associated with the DDI must be determined, including the magnitude, variability and frequency of effects (if known), and modifying factors that may increase or decrease the risk of patient harm (see Figure 1). Depending on the context, exposure to a clinically relevant DDI might warrant a change in therapy, increased monitoring, and/or patient education. Assessing the clinical relevance of a DDI is an estimate, at best, because inter-patient variability is often unknown, and for PK DDIs, changes in the object drug can vary 4–6-fold [46, 47]. For some DDIs, it is reasonable to assign a general risk rating based on the properties of the object drug, such as those with a NTI.

We recommend providing estimates of the frequency (incidence) of adverse outcomes from DDIs when available. However, assessing these frequencies is difficult because data are largely limited to observational studies, which are susceptible to confounding. When available, the definition of the adverse outcome and the applicable population should be clearly specified. For example, we can inform patients that the risk of upper gastrointestinal (GI) bleeding is estimated to increase by 19% with combined use of selective serotonin reuptake inhibitors (SSRIs) and nonsteroidal anti-inflammatory drugs (NSAIDs) beyond the effects of each individual drug [48]. We can also estimate that 179 (95% CI = 107,319) high-risk patients (e.g., elderly, previous GI bleed) and 645 (95% CI = 387, 1,152) low-risk patients need to be treated with the SSRI and NSAID combination to cause one upper GI bleed [48]. But for most DDIs—even those that are well-documented and potentially dangerous—only rough estimates of the incidence of adverse outcomes are known.

Thorough evidence evaluation of DDI literature should include documented methods to mitigate harm (e.g., dosage adjustment, monitoring strategies, and therapeutic alternatives) [22, 49]. Reasonable therapeutic alternatives may include DDIs ruled out by mechanistic principles, preferably with one or more negative studies that appear robust to bias and confounding.

We also recommend that modifying factors that may increase (risk factors) or decrease (mitigating factors) susceptibility to DDIs should be considered when evaluating and reporting DDI evidence. Drug-related modifying factors may include dose, duration, route of administration, order of administration, timing of dose, and comedications. Patient-related modifying factors may include age, sex, pharmacogenomics [50], comorbidity, clinical status, vital signs, laboratory values, and indication for the drug. Identifying modifying factors is essential because research shows that providing patient-specific risk factors in CDS improves the specificity of alerts [51, 52]. There are many situations where a particular DDI may not be clinically relevant to a specific patient due to mitigating factors that result in a negligible risk of adverse outcomes. For example, a precipitant drug is unlikely to produce a clinically relevant DDI for a patient with a genetic variant producing a nonfunctional CYP enzyme (i.e., poor metabolizer) [53]. However, information on factors that alter patient susceptibility to DDIs is not yet systematically reviewed in DDI guidelines [52]. In general, more research is needed to identify modifying factors to inform CDS algorithms and clinical decision-making.

More work is also needed to identify the most appropriate process to rate the quality of DDI evidence and provide graded recommendations to reduce the risk of adverse consequences [49]. We recommend considering the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system, a well-accepted standard to indicate quality of evidence and strength of recommendations [54–57].

3.3 Key Question 2: What evidence is required for a DDI to be applicable to an entire class of medications?

CDS systems can generate nuisance alerts when they inappropriately define or represent a DDI as a “class” effect. Knowledge of the mechanism of interaction is crucial to determining whether there is basis for a class effect. Most class-based DDIs are of a PD

nature, with additive (e.g., angiotensin-converting enzyme (ACE) inhibitors + angiotensin II receptor blockers (ARBs)) or opposing (e.g., beta blocker + beta agonist) pharmacologic effects. In contrast, PK interactions are rarely generalizable to all agents within a class [22, 58]. Even when there is seemingly a class effect, the magnitude of effect can vary, which often makes it necessary to consider each drug in the class individually. For example, azole antifungal agents can inhibit cytochrome P450 (CYP) 3A4. However, itraconazole and ketoconazole are much more potent inhibitors than fluconazole, so the magnitude of interaction with drugs that are primarily metabolized by CYP3A4 may differ significantly, which would impact the clinical relevance of the interaction. This can be shown by their effect on triazolam levels: itraconazole and ketoconazole increase the AUC of triazolam by 27- and 22-fold, respectively [59], whereas fluconazole causes a 4.4-fold increase in AUC [60].

The overwhelming majority of extrapolated DDIs are PD, because few studies are conducted to investigate this type of interaction. In the absence of drug-specific data, a class-based interaction may be reasonably assumed if the purported mechanism of interaction is biologically plausible and consistent with known pharmacology of one or both classes of drugs involved. Class examples include SSRIs + other serotonergic drugs related to serotonin syndrome and anticoagulation + antiplatelet agents related to bleeding.

Occasionally, PK interaction data may be extrapolated from one agent to other agents in the class if the purported mechanism of interaction involves common pharmacologic effects. For instance, NSAIDs may reduce the renal excretion of lithium and therefore increase the risk of toxicity [61]. The proposed mechanism of interaction is inhibition of renal prostaglandin synthesis by NSAIDs, which leads to reduced renal blood flow. Although lithium toxicity has not been reported with all NSAIDs, the interaction is probably applicable to the entire class based on their common ability to inhibit prostaglandin synthesis.

We recommend that DDIs should be class-based only when the evidence (or reasonable extrapolation) applies to the entire pharmacological class of drugs.

3.4 Key Question 3: How should a structured evaluation process be vetted and validated?

In Key Question 1, we recommended use of a new instrument as a standard to evaluate DDI evidence. However, any new DDI evidence evaluation instrument should undergo a rigorous evaluation. The evaluation should ensure that the instrument is easy to apply by end users and produces results that are generally concordant with other DDI evidence rating systems, except where differences are expected.

We recommend evaluating the new DRIVE Instrument using a subset of 15 “high-priority” DDIs (drug pairs which should always generate an alert) approved by an ONC-commissioned panel of experts [62]. There are also several existing studies that have systematically collected evidence for a set of DDIs and then examined concordance on DDIs mentioned in drug information sources [12, 35, 40, 42, 63]. These studies can provide DDIs for which there are varying degrees of agreement across drug information sources (e.g., some DDIs that all sources mention and others that only one source mentions).

4 Discussion

This expert panel was convened to recommend an approach for evaluating DDIs in order to provide consistent, evidence-based CDS systems for healthcare providers. Because of the numerous challenges to evaluating evidence for DDIs, we propose a systematic and transparent process to evaluate evidence that supports the existence of clinically relevant DDIs. Furthermore, the use of a standardized evidence-based approach to evaluate DDI evidence will eliminate combinations with a low probability of harm and minimize legal liability for knowledgebase vendors and healthcare systems [23].

Our search for relevant tools to evaluate the DDI evidence identified no instruments that possessed all of the attributes believed to be important. Consequently, we developed DRIVE for evaluating the body of evidence for DDIs using important concepts from existing evidence evaluation methods with a focus on simplicity and explicit criteria for certain types of evidence [31, 32]. In this process, we defined several terms for use when evaluating DDIs because consistent application of terminology is requisite for systematic evaluation.

We recommend that any systematic approach to evaluating DDI evidence be validated to ensure the method is worthwhile. To that end, further evaluation of the DRIVE approach, including explicit criteria for what constitutes a well-designed and executed study should be developed. We recommend that DDI evidence reported in product labeling should be evaluated by the same criteria as published studies to establish sufficiency of DDI evidence.

For case reports, we judged the DIPS to be the most appropriate published method to evaluate whether a DDI occurred [20]. Case reports may provide the first evidence of DDIs; however, using these reports as the sole evidence source has several disadvantages. They are often poorly described, leading to speculation and potentially inaccurate inferences about causal relationships. Use of case reports that are later found to be incorrect results in erroneous data listed in prescription product labeling and/or drug information compendia that are very difficult to correct. Therefore, careful evaluation of case reports is needed to establish the existence of a DDI.

We accomplished our goal of identifying principles for establishing a systematic process for evaluating evidence for DDIs; however, more work remains in certain areas. Although the DRIVE instrument may be used in the future to affirm that a DDI exists, further evaluation is needed to establish criteria for assessing clinical relevance. This entails identifying the associated clinical effects and their magnitude, variability, and estimated frequency. Modifying factors that may increase or decrease the risk of patient harm should also be identified. Pharmacogenetic research can further improve the precision of DDI evidence and CDS by identifying patient-specific predisposing factors. More work is also needed to identify the most appropriate process to rate the quality of DDI evidence and provide graded recommendations to reduce the risk of adverse consequences [49]. We recommend considering the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system, a well-accepted standard to indicate quality of evidence and strength of recommendations [54–57].

5. Conclusion

Stakeholders—such as editors, developers, and end users of CDS software and compendia—should require consistent application of transparent, systematic methods to assess DDI evidence. We envision these recommendations improving the evaluation of DDI evidence for CDS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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KEY POINTS

- Evidence-based clinical decision support for drug-drug interactions (DDIs) requires consistent application of transparent and systematic methods to evaluate the evidence.
- An expert workgroup developed recommendations by consensus for systematic evaluation of evidence for DDIs from the scientific literature, drug product labeling, and regulatory documents.
- Workgroup members expect that drug information systems will be able to provide higher quality information about DDIs in drug compendia and clinical decision support tools.

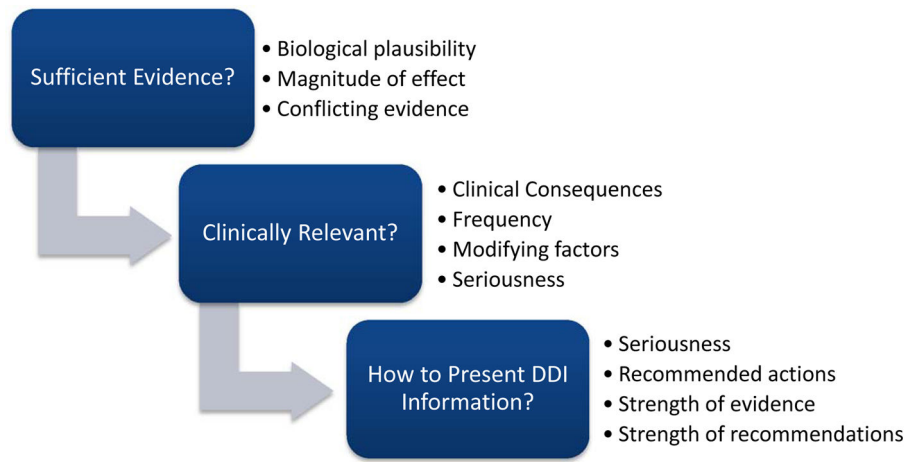


Figure 1. Conceptual Model for Evaluating Drug-Drug Interactions to Guide Clinical Decision-Making

Table 1

Summary of Evidence Workgroup Recommendations for Systematic Evaluation of DDI Evidence

Recommendation	Comments
<i>Recommendations to be Adopted in the Short Term</i>	
Apply consistent terminology	<ul style="list-style-type: none"> Terminology defined by the Evidence Workgroup is provided in Appendix A.
Apply DIPS for evaluating DDI case reports [20]	<ul style="list-style-type: none"> DIPS guides users to conduct an explicit, transparent, complete, and balanced assessment of the attributes important to causality assessment of whether a DDI occurred and exists [30].
A new approach for evaluating a body of evidence	<ul style="list-style-type: none"> DRIVE was developed based upon important concepts from existing methods [31, 32] with modification to: (1) use simple evidence categories; (2) include causality assessment with DDI case reports (via DIPS); (3) apply reasonable extrapolation, including from <i>in vitro</i> studies; and (4) address evidence/statements provided in product labeling; and (5) describe study quality criteria and interpretation in the context of DDIs.
Evaluate statements/evidence in FDA documents and product labeling by same criteria as published evidence	<ul style="list-style-type: none"> DDI recommendations provided in labeling that are not supported by PK data or PD properties of the drugs are insufficient evidence. DDI listings/recommendations in CDS systems do not need to align with unsupported statements in product labeling.
Classify DDIs by therapeutic/pharmacologic class only when the evidence applies, or can be reasonably extrapolated, to the entire class of drugs	<ul style="list-style-type: none"> Class effects distinction commonly apply to PD DDIs, but rarely to PK DDIs.
<i>Recommendations for Future Work</i>	
Evaluate DRIVE Instrument	<ul style="list-style-type: none"> Testing should include (1) usability; (2) inter-rater agreement, (3) concordance (where expected) with similar systems [31, 32]; and evaluation of DIPS for case reports [20].
Develop systematic DDI search criteria	<ul style="list-style-type: none"> See examples by <i>Boyce et al.</i> [33–35]. Search should include unpublished literature, including FDA preapproval reviews and post- marketing analyses [36, 37]. Search criteria are needed to identify evidence for: (1) the existence of a DDI; (2) clinical outcomes, including frequency and modifying factors; and (3) clinical management (e.g., monitoring, dosage adjustments, and therapeutic alternatives).
Identify or develop a system to evaluate and communicate the strength of DDI evidence with graded recommendations [49]	<ul style="list-style-type: none"> The GRADE approach is endorsed or used by numerous organizations (e.g., AHRQ, Cochrane Collaboration, WHO) [54–57]. A modified GRADE approach is used by the University of Liverpool for evidence of DDIs involving medications for HIV and hepatitis C [64, 65].

AHRQ = Agency for Healthcare Research and Quality; CDS = clinical decision support; DDI = drug-drug interaction; DIPS = Drug Interaction Probability Scale; DRIVE = DRug Interaction eVidence Evaluation (DRIVE); FDA = Food and Drug Administration; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; PD = pharmacodynamics; PK = pharmacokinetic; WHO = World Health Organization