Drug-Drug Interaction Alerts: Emphasizing the Evidence

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DRUG-DRUG INTERACTION ALERTS: 
EMPHASIZING THE EVIDENCE

SHARONA HOFFMAN* AND ANDY PODGURSKI**

INTRODUCTION

Many analysts and users of contemporary clinical decision support ("CDS") systems have expressed grave concerns about the technology's efficacy and functionality.1 Alerts generated by CDS systems are often inaccurate, and an excess of alerts, especially those of dubious quality, leads some physicians to experience "alert fatigue" and to turn off CDS altogether.2 Susan Ridgely and Michael Greenberg undertake an important project in formulating recommendations to promote CDS improvements.3 They have written a thoughtful and well-researched article that focuses on drug-drug interaction ("DDI") alerts, and they correctly identify liability concerns as a hindrance to the alerts’ optimal implementation.4

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1. Kim R. Saverno et al., Ability of Pharmacy Clinical Decision-Support Software to Alert Users About Clinically Important Drug–Drug Interactions, 18 J. AM. MED. INFORMATICS ASS’N 32, 35 (2011) ("This CDS software evaluation study provides insight into the poor performance of pharmacy systems in alerting pharmacists of clinically significant drug interactions."); Randy C. Hatton et al., Evaluation of Contraindicated Drug-Drug Interaction Alerts in a Hospital Setting, 45 ANNALS PHARMACOTHERAPY 297, 298 (2011) ("Drug-drug interaction alerts have been shown to be often misclassified, and the importance of many of these supposed interactions has been questioned.").


4. Id.; Hatton et al., supra note 1, at 305-06; Saverno et al., supra note 1, at 36.
Ridgely and Greenberg outline a five-part strategy to diminish liability concerns and thereby promote CDS improvements. We will critique the primary elements of their proposal and formulate several original recommendations.

In general, Ridgely and Greenberg call for the development of a consensus-based “clinically significant drug-drug interaction list” that could generate limited liability protection for users. DDIs have been defined elsewhere as “drug combinations resulting in pharmacological or clinical response, which differs from responses to the agents when either is given alone,” and “clinically important” DDIs have been described as those “most likely to cause harm if not detected.”

Ridgely and Greenberg do not fully explain what they mean by a clinically significant DDI list, and thus, their liability protection proposal is somewhat difficult to assess. Would the list consist only of DDIs that are always contraindicated? Would the list include DDIs that will adversely affect only some patients? Will alerts provide prescribers with information that will enable them to determine whether the drug combination can or cannot be safely prescribed to particular patients?

In Part I we address the notion of a clinically significant DDI list. We support efforts to eliminate excessive DDI alerts and to reach consensus as to which DDIs should generate alerts. However, a simple list of drug combinations that are always contraindicated would not go far enough and could, in some circumstances, be misleading because it would ignore the complexity and highly individualized nature of most treatment choices. Instead, DDI warnings should provide users with concise but comprehensive information that will enable them to make more knowledgeable and effective prescribing decisions. Thus, from both clinical and malpractice liability perspectives, it is important that DDI alerts offer essential information about DDI risks, supporting evidence, mitigating factors, and appropriate courses of action.

In Part II, we analyze the process for determining which DDIs should generate alerts in CDS systems. We agree with Ridgely and Greenberg’s recommendation that experts who represent a variety of professional organizations be tasked with developing DDI alert information, but we argue

5. Ridgely & Greenberg, supra note 3, at 264.
8. See infra p. 299.
9. See infra p. 303.
that the government must play a key role in the process. In Part III we assess the use of DDI alert compliance data as evidence in malpractice litigation and as a basis for liability protection.

I. CRAFTING USEFUL DDI ALERTS

Ridgely and Greenberg are right to identify alert fatigue and the resulting tendency of physicians to turn off DDI alerts as endangering patient welfare. To address this problem, they seek to limit the number of alerts that physicians receive and to assure prescribers about the alerts’ reliability. Their proposal is anchored in the creation of a list of clinically significant DDIs that experts and the government will endorse and that CDS-system vendors will routinely include in their systems. In this section we argue that a list of drug combinations that are consistently contraindicated would not provide much, if any, benefit to clinicians and patients. We also formulate recommendations for an alternative approach to DDI alerts.

A. Feasibility of a National DDI List

A shortcoming of the Ridgely and Greenberg article is that they do not explain what they mean by a “clinically significant DDI list.” If what they mean is a list of drug combinations that are inappropriate in all circumstances, which we will call “always contraindicated DDIs,” such a list would be of limited use because it could not adequately reflect the complexity of many treatment decisions. The risk of DDIs often varies from patient to patient and could be influenced by factors such as an individual’s age, sex, kidney function, liver function, genetic makeup, and disease, as well as by the medication’s dose and route of administration. Furthermore, sometimes the risks of a DDI must be tolerated because the benefits of a drug combination outweigh them, and physicians will manage

10. Ridgely & Greenberg, supra note 3, at 264; see infra pp. 303-5.
11. See infra p. 306.
12. Ridgely & Greenberg, supra note 3, at 258; van der Sijs et al., supra note 2, at 447 (concluding that “hospital-wide DDI alert suppression” is not advisable).
13. Ridgely & Greenberg, supra note 3, at 262.
14. Id. at 279.
15. Id.
the risks by monitoring the patient carefully in order to prevent harm. One source provides the example of patients with both coronary artery disease and atrial fibrillation who “may require ASA to prevent myocardial infarction and warfarin for stroke prevention” even though these are two interacting drugs.

Moreover, there is insufficient scientific evidence as to which DDIs truly create severe risks for patients. Thus, even a group of highly qualified experts are unlikely to agree upon a list of always-contraindicated DDIs. A variety of sources can provide DDI information, but the data is often inconsistent or unreliable. The sources include manufacturers’ drug pamphlets, several drug compendia, articles in the medical literature, medical databases, and clinical experts. Papers and clinical trials that claim to establish the existence of interactions may be of varying quality, and in some instances, interactions are assumed based only on theory and analogy. Researchers have not thoroughly studied many drug combinations, and the major drug compendia often differ as to which DDIs are worth listing and as to their severities.

One study focused on 458 drug pairs and found that proprietary databases rated 7.4% of interactions (34/458) as severe, and clinicians assessed 6.6% (30/458) as severe, but only three interactions were considered severe by both the databases and clinicians. A different study used a panel of experts to evaluate DDIs and found that the experts initially agreed “on the clinical significance of an interaction approximately 50% of the time.”

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17. Reimche et al., supra note 6, at 1047.
18. Id.
19. Hatton et al., supra note 1, at 298.
20. Malone et al., supra note 7, at 144 (naming the following DDI compendia, Evaluation of Drug Interactions, Drug Interaction Facts, Drug Interactions: Analysis and Management, and MICROMEDEX: (DRUG-REAX), and noting that they “provide inconsistent classification to determine which interactions are clinically important”).
21. Id.
22. van Roon et al., supra note 16, at 1133.
23. Id. at 1134.
24. Saverno et al., supra note 1, at 35.
26. Id. The three were atazanavir-simvastatin, atazanavir-tenofovir, and aspirin-warfarin.
Even if experts could formulate a list of always-contraindicated DDIs, the list would probably be very short and would fail to provide physicians with significant prescribing guidance. One project, which evaluated DDI alerts based on a literature review and the opinions of an expert panel, concluded that only 15.3% of the DDI alerts studied “were for medications that should never be used together.”

A study of four drug interaction compendia revealed that only 2% of the major known interactions were found in all four.

B. Constructing Useful DDI Alerts

In our view, an approach that provides physicians with information that enables them to assess the desirability of prescribing potentially interacting drug combinations would be far superior to a rigid DDI list, with respect to both medical benefits and reduction in liability risks for providers and CDS-system vendors. In the majority of cases, there is no certainty that a patient will suffer an adverse consequence from a DDI, rather, there is only some risk that this will happen.

The Netherlands has developed a model that could be emulated in the United States. DDI alerts provide users with text that assists them in managing interactions, and the text can be tailored to different types of providers: prescribers, pharmacies, and hospitals. Prescribers are given information about alternative drugs and ways to adjust patient monitoring. Users can also consult general background material for information about: (1) evidence of the DDI; (2) clinical relevance of the possible adverse DDI consequences; (3) specific risk factors associated with patient characteristics, the disease, and the drug; and (4) the adverse reaction’s rate of incidence. The text also discusses the mechanism of interactions and briefly summarizes the literature addressing the DDI, and simple codes indicate the quality of the evidence and the seriousness of the adverse outcome (e.g. “4F” – high quality published evidence and very clinically relevant adverse reaction).

A similar approach could be adopted in the United States. In lieu of a national DDI list, providers should have access to well-presented, concise information that will enable them to make appropriate decisions about the

(finding that “there was no universality in the severity rating scales for drug interactions used by the drug information software programs”).

29. Saverno et al., supra note 1, at 35-36.
30. See Malone et al., supra note 7, at 144.
31. van Roon et al., supra note 16, at 1136.
32. Id.
33. Id. at 1133, 1136.
34. Id. at 1136.
treatment of their particular patients. Patient data stored in electronic health records ("EHR") should play a vital role in determining when DDI warnings will be issued. Such data is essential in many cases both to triggering appropriate warnings and to preventing inappropriate warnings. In general, both the risk of an adverse drug reaction due to a DDI and the quality of the evidence concerning the risk may depend on a number of patient-specific risk factors, some or all of which may be recorded in a patient’s EHR.35 If information about particular risk factors is absent from the EHR, the CDS system should prompt for it by suggesting that doctors conduct further testing or question patients about it. It is important to note that the reliability of DDI alerts will also depend on the accuracy of the data in patients’ EHR, which may be compromised by input errors, omissions, and other problems.36

In addition, experts could develop codes that accompany DDI alerts, indicating the quality of the evidence (including patient-specific factors) for an adverse DDI reaction and the severity of the potential adverse reaction (e.g. 4F).37 According to the medical literature, there is evidence that tiering or stratifying DDIs by severity increases prescriber compliance with alerts.38 Having seen the code and the initial warning text, users should be able to click on the alert to access more detailed information that appears in a concise and easily understandable form. Ideally, clinicians would always look at the additional material, but in some cases, prescribers may feel that they are familiar with both the DDI and the particular patient and are too busy to read the literature summaries. A quick glance at the code would enable them to confirm their conclusion or prompt them to further investigate the potential adverse outcome.

Since many DDIs are influenced by multiple risk factors, experts may not be able to enumerate the risk levels and quality of evidence associated with


37. See infra p. 306, for discussion of the role of experts.

every possible combination of risk factors for each DDI. The total number of such combinations could be very large. However, it may be possible for experts to develop an algorithm or a statistical model (or set of models) for predicting a patient’s risk for an adverse DDI based on appropriate risk factors and strength of evidence.39

Alert fatigue should not be addressed by allowing doctors to suppress or turn off alerts because such options may cause doctors to miss critical warnings altogether.40 Turning off alerts could thus compromise patient care and increase liability exposure for doctors. Warnings should be noticeable but unobtrusive and should not be time-consuming or complicate physicians’ EHR work. A doctor who has previously received the same warning but knows her patient tolerates the medications well should not have to spend significant time processing the alert. Further discussion of the user interface is beyond the scope of this article, and the technical design of DDI alerts will require the skill of highly qualified experts.

No extensive list of always-contraindicated DDIs is likely to be developed. In most cases, DDI alerts can at best provide prescribers with information that facilitates their decision-making process. Improved design and usability of alerts would not only provide prescribers with more accurate and helpful information, but also reduce clinicians’ frustration and alert fatigue. In addition, it is critical for vendors of CDS systems to eliminate excessive DDI warnings. To that end, professional organizations and the federal government could provide expert input, oversight, and even regulatory guidance for DDI alerts, as detailed in the following section.

II. EXPERT INPUT

Ridgely and Greenberg wisely call for a national expert process to develop DDI alert information.41 At this time in the United States, vendors of CDS systems generally rely on various commercial databases or “knowledge bases” to create their DDI alerts,42 and many commentators have noted that

40. See van der Sijs et al., supra note 2, at 447 (suggesting that turning off alerts may pose dangers to patient welfare).
41. Ridgely & Greenberg, supra note 3, at 279.
42. Smithburger et al., supra note 25, at 1719 (discussing the Micromedex and Lexi-Interact databases); Hatton et al., supra note 1, at 299 (discussing DDIs “from a commercial knowledge base vendor”); Nidhi R. Shah et al., Improving Acceptance of Computerized Prescribing Alerts in Ambulatory Care, 13 J. AM. MED. INFORMATICS ASS’N 5, 5 (2006) (“Many CDS use commercial knowledge bases to drive their alerting”).
the performance of DDI alert systems is disappointing and inconsistent.\textsuperscript{43} Furthermore, CDS-system vendors and knowledge-base vendors tend to generate excessive warnings in order to minimize their own risk of liability, and such practices lead to alert fatigue and ultimately can compromise patient care.\textsuperscript{44}

The efficacy of DDI alerts could be significantly improved through input from clinical experts, as suggested by Ridgely and Greenberg.\textsuperscript{45} We agree with the authors that any credible expert process would have to include representatives of a broad range of professional organizations.\textsuperscript{46} However, we question their suggestion that participation by government officials may be inadvisable.\textsuperscript{47}

The Dutch have recognized the importance of broad-based expert input and cooperation between experts and government authorities.\textsuperscript{48} The Working Group on Pharmacotherapy and Drug Information is a twenty-two member multidisciplinary body that includes internists, general practitioners, pharmacists, and a member of the Netherlands Medicines Evaluation Board.\textsuperscript{49} The Working Group is responsible for maintaining the Royal Dutch Association for the Advancement of Pharmacy’s computerized drug interaction surveillance systems and for selecting which DDIs will be included.\textsuperscript{50}

The authors note that the Department of Health and Human Services’ Office of the National Coordinator (“ONC”) has already instituted a project called \textit{Advancing Clinical Decision Support} tasked with formulating a clinically significant DDI list.\textsuperscript{51} The authors provide no details concerning this initiative, and a search of the Internet revealed little illuminating information.\textsuperscript{52} If \textit{Advancing Clinical Decision Support} does not produce satisfactory results, ONC could establish a federal advisory committee, similar to the existing Health Information Technology (“HIT”) Policy

\textsuperscript{43} Smith et al., supra note 27, at 47; Jacob Abarca et al., \textit{Evaluation of the Performance of Drug-Drug Interaction Screening Software in Community and Hospital Pharmacies}, 12 J. MANAGED CARE PHARMACY 383, 388 (2006).

\textsuperscript{44} See supra note 2 and accompanying text.

\textsuperscript{45} Ridgely & Greenberg, supra note 3, at 279; see also Zopf et al., supra note 35, at 795 (discussing the need for input from an international expert panel).

\textsuperscript{46} See Ridgely & Greenberg, supra note 3, at 280.

\textsuperscript{47} See id.

\textsuperscript{48} See van Roon et al., supra note 16, at 1132.

\textsuperscript{49} Id.

\textsuperscript{50} Id.

\textsuperscript{51} Ridgely & Greenberg, supra note 3, at 259.

\textsuperscript{52} See \textit{Advancing Clinical Decision Support}, RAND HEALTH, http://www.rand.org/health/projects/clinical-decision-support.html (last visited Jan. 20, 2012) (internet searching yields the project website, which in turn lists only the project’s four tasks, without providing further details on goals, method, or timeline).
Committee and the HIT Standards Committee, which would include individuals with significant medical and pharmacological expertise.53

Any group tasked with developing DDI alert rules should be composed of representatives of professional medical and pharmacy associations, including clinicians who use CDS, as well as government officials, such as Food and Drug Administration (“FDA”) employees with DDI expertise. The expert panel we envision would assemble, vet, and distill relevant medical knowledge about DDIs into forms that meet the needs of physicians and are amenable to use with CDS systems. As discussed above, the panel would determine which DDIs require alerts, what evidence is reliable, and what material should be compiled for CDS users, and it could develop DDI severity codes or coding algorithms. All DDI information would need to be updated regularly as new research findings emerge. The panel could also help to identify knowledge gaps that the federal government could address with targeted research funding.

Developing and updating DDI information will require a tremendous amount of effort. Ridgely and Greenberg recognize that professional organizations may be unable to undertake or sustain the project without government support, and we believe that ONC involvement would be critical.54 ONC would need to motivate, organize, and fund the DDI initiative. Because the value of DDI alerts has yet to be proven, even a body of rules developed by top experts should not be widely deployed without clinical testing that includes the targeted end-users (e.g. primary care physicians, particular specialists, etc.). The rules should be piloted in a number of representative settings to determine whether they are effective in promoting improved prescribing decisions and are not overly disruptive to the users. Once the merit of the DDI rules has been proven, ONC could incorporate the rules into future meaningful use and certification regulations, as Ridgely and Greenberg suggest.55 Additional or revised rules could be incorporated periodically through a similar process. Regulatory endorsement of particular DDI rules would remove vendors’ incentive to include other, superfluous DDI alerts that subject prescribers to information overload.

54. Id.
55. Id. at 286.
The Netherlands system provides an illuminating case study of the efficacy of a central DDI authority.56 According to a 2005 report, the Dutch Working Group reviewed 244 drug combinations that were initially included in CDS systems and determined that only 160 of them actually required alerts.57 A 2008 study confirmed that the Dutch drug database was not overly inclusive, but it nevertheless found that physicians continued to complain of alert fatigue and wished to suppress some of the warnings.58 Perhaps no DDI alert system will satisfy all users, and policy-makers will need to continue to learn about and refine this emerging technology. Thoughtful input from national experts, however, could contribute significantly to improvements of the widely criticized contemporary systems.

III. DDI ALERT USE AS EVIDENCE IN LITIGATION

Ridgely and Greenberg offer an additional suggestion to promote the acceptance of an authoritative DDI list.59 They argue that government intervention in the form of liability protection is needed to incentivize implementation and use of a national DDI list.60 To that end, they argue that federal legislation should create a legal “safe harbor” to protect physicians who make treatment decisions using a consensus-based DDI list.61 The safe harbor clause would establish that a clinician’s choice not to adopt more extensive DDI alerts could not be used against her as evidence of negligence or as a basis for liability.62 The authors suggest that such immunity should also extend to hospitals and health care organizations.63 Furthermore, the safe harbor provision should establish that CDS system vendors will not be vulnerable to liability for allowing users to modify the scope of DDI alerts.64 Finally, Ridgely and Greenberg recommend that the FDA begin regulating medical software as a Class III device so that FDA approval will preempt state court tort actions against vendors pursuant to the Supreme Court’s Riegel v. Medtronic decision.65

In our view, whether or not a safe harbor provision is sensible depends on what Ridgely and Greenberg mean by a “clinically significant DDI list.” If

56. See van Roon et al., supra note 16, at 1137-8.
57. Id. at 1137.
58. van der Sijs et al., supra note 2, at 447.
59. Ridgely & Greenberg, supra note 3, at 290.
60. Id.
61. Id.
62. Id.
63. Id.
64. Ridgely & Greenberg, supra note 3, at 292.
65. Id. at 31-2; see Riegel v. Medtronic, Inc., 552 U.S. 312, 323, 330 (2008) (holding that FDA premarket approval preempts state common law claims challenging the safety or effectiveness of a medical device marketed in the approved form). UPDATE
this is a list of always-contraindicated DDIs, it is likely to be quite short and minimal. Thus, it would be inappropriate to grant providers immunity based on their choice to use only the listed DDI alerts. However, if an expert panel or a federal advisory committee were to develop a comprehensive body of DDI alert rules, adoption of Ridgely and Greenberg’s safe harbor proposal would be reasonable. Carefully developed and continually updated DDI alert rules that were endorsed by ONC and perhaps even incorporated into federal regulations would justify protecting providers from liability based on their decision to decline to receive additional DDI alerts.

At the same time, we must emphasize that providers should never enjoy immunity based simply on following particular DDI alerts. Clinicians should receive DDI information through alerts but generally cannot be given complete instructions as to how they should proceed. DDI alerts should be advisory only, and doctors should apply their medical judgment to determine the appropriate course of action. Patients who suffer harm because of physician negligence should not be barred from seeking redress.

The courts will need to determine the extent to which a provider’s use of DDI alert information or deviation from alert recommendations could be introduced as evidence in court. Parties might also be able to use evidence concerning the reliability of particular DDI alerts in litigation. For example, studies that review DDI alerts in light of the contents of patient EHRs at the time might reveal that particular DDI alerts have high rates of false positives (false alarms). A false positive would be an alert that indicates that there is strong evidence of severe harm to patients when in truth, few patients suffer adverse consequences from the particular drug combination. This evidence might be used in defense of a physician’s decision to disregard an alert. As an added benefit, collection of data about false positives, false negatives, and related statistics would generate valuable information about the efficacy of DDI alerts. Such information could be systematically studied by ONC and used to refine future DDI alert rules.

The authors’ suggestion that the FDA regulate CDS software as a Class III device requires further qualification. Class III devices are not always...

66. See supra p. 299.
67. See supra p. 301.
68. See R.A. Miller, Legal Issues Related to Medical Decision Support Systems, 6 INT’L J. CLINICAL MONITORING & COMPUTING 75, 78-79 (1989); see also Hoffman & Podgurski, E-Health Hazards, supra note 36, at 1548 (discussing admission of evidence in cases where physicians failed to take DDI warnings into account).
69. A false negative would occur if no DDI alert were generated, but a patient nevertheless experienced an adverse reaction to a drug combination.
70. See van Roon, supra note 16, at 1137 (discussing how evaluation of data enabled the Dutch Working Group to eliminate some DDIs from CDS alerts).
subject to rigorous FDA pre-market approval. Rather, twenty-six Class III device types are reviewed under the much more lenient 510(k) process.\footnote{71. INST. OF MED., MEDICAL DEVICES AND THE PUBLIC’S HEALTH: THE FDA 510(k) CLEARANCE PROCESS AT 35 YEARS 100-01 (2011).} The Institute of Medicine recently issued a report that found the 510(k) process to be sorely inadequate and recommended that it be replaced by more effective review procedures.\footnote{72. See id. at 6-8.} Class III classification alone, therefore, does not automatically lead to pre-market approval and to the associated liability protection under \textit{Riegel}.

FDA regulation would be acceptable only if CDS software were consistently subject to thorough pre-market approval and then to careful post-market monitoring, including mandatory reporting of all adverse events.\footnote{73. See \textit{Medtronics, Inc.}, 552 U.S. at 323 (describing the FDA's approval and reporting requirements for Class III devices).} In prior work, we have emphasized the critical importance of clinical testing and effective review procedures for EHR systems before they are deployed in the market and of rigorous post-market surveillance.\footnote{74. Sharona Hoffman & Andy Podgurski, Finding a Cure: The Case for Regulation and Oversight of Electronic Health Record Systems, 22 HARV. J.L. & TECH. 103, 143-50 (2008).} Such oversight mechanisms are particularly crucial for CDS software, because it can directly influence treatment decisions.\footnote{75. Adam Wright et al., Governance for Clinical Decision Support: Case Studies and Recommended Practices from Leading Institutions, 18 J. AM. MED. INFORMATICS ASS'N 187, 187 (2011).}

\textbf{CONCLUSION}

Ridgely and Greenberg propose thoughtful recommendations to improve DDI alerts by addressing vendors’ and providers’ tendencies to adopt excessive warnings in light of liability concerns. The authors wisely suggest that DDI alerts be overseen by a uniform expert process and that the product of such a process be incorporated into federal regulations. A limited liability shield may also be implemented to induce vendors and providers to adopt the federally endorsed DDI rules. We have emphasized that experts should develop flexible DDI alert rules rather than a rigid DDI list. Furthermore, alerts must provide prescribers with comprehensive information and be considered advisory in nature. Physicians must retain their discretion to interpret information and decide whether to comply with or reject recommendations. Physicians would likely find an alert system that respects their judgment more palatable than one that assumes they will practice medicine by formula, and patients would likely prefer that their
doctors continue to use their discretion and tailor treatment protocols to individual circumstances.

The efficacy of CDS systems has been questioned by many researchers and commentators.76 We commend continued efforts to grapple with the limitations of current CDS technology and to find the right balance between over- and under-inclusiveness of alerts. We are hopeful that ultimately CDS will prove to be a reliable resource for clinicians and facilitate significant improvements in treatment outcomes.

76. See, e.g., Hoffman & Podgurski, E-Health Hazards, supra note 36, at 1546-47 (discussing several researchers’ results and findings).