The Problem with the Drug–Drug Interaction Software: A Procrustean Dilemma

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Abstract

This chapter discusses the risks of relying exclusively on drug–drug interaction software.

When the ancient Greek hero, Theseus, travelled to Crete, he encountered and vanquished several formidable foes. One of these was Procrustes. Procrustes's modus operandi was to invite guests into his home and, after lavishly feeding them, insist that they sleep in one of his beds. But there was a catch. If the guest was tall, Procrustes would take him to a short bed and insist on cutting off his legs so he would fit. Alternatively, if the guest was short, he would take them to a long bed and stretch them on a rack until they fit. Procrustes's guests were a uniformly unhappy lot, until Theseus turned the tables and subjected Procrustes to his own hospitality.

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Physicians and other health care providers who have acknowledged and undertaken the need to incorporate a knowledge and mastery of perioperative drug–drug interactions (DDIs) in their daily practice face a crucial question. It is a given that the information imparted in a few lectures in medical school and a few more in training is simply not enough to maintain excellence and currency in clinical practice. How then and by what means do responsible clinicians augment and sustain their working knowledge base? Can a clinician rely solely on the widely available commercial and institutional software for the identification and avoidance of the DDIs that will keep her patients safe and free from undue clinical events?

We believe the answer is no.

In spite of diligent efforts, the designers of DDI computer programs are in a quandary that would be familiar to the guests of the mythical Procrustes. For that reason, we do not recommend either an overconfidence or overreliance on DDI computer software.

Of course, we do not mean to imply that DDI software programs can or should be ignored or even significantly discounted. They can be helpful and they are here to stay. But the evidence base on DDI software programs, and e-prescribing in general, although still young and fairly scant, is not entirely favorable. Weingart et al. performed a survey of ambulatory care physicians to characterize assessments of an e-prescribing system with allergy and drug interaction alerts.[1] Although physicians indicated that e-prescribing improved the quality of care and prevented medical errors overall, they were much less positive about alerts triggered by discontinued medications, alerts that failed to account for appropriate drug combinations, and an excessive number of alerts. A second paper by Weingart et al. acknowledged that ambulatory care clinicians override as many of 91% of drug interaction alerts and reported the development of an empirical model to estimate the potential impact of medication safety alerts.[2] They concluded, in part, that preventing drug interactions saves lives and health care dollars, however, 331 alerts were required to prevent one adverse drug event. A third paper by Isaac et al. concluded "Clinicians override most medication alerts, suggesting that current medication safety alerts may be inadequate to protect patent safety."[3]

Why and what situations does this happen? The problem is evident when considering the situation of a hypothetical clinician who wants to add a potential drug to the regimen of a medically complex patient. She searches her memory of the subject and finds nothing. She types the new prospective regimen into an internet drug interaction program, and is then faced with a lengthy collection of potential interactions. The vagueness of these designations and the breadth of the list makes it difficult to judge. She asks the person next to her what they would do. They shrug. She gazes at the list of DDIs again. She then is tempted to just shut the thing off, go for it, and hope for the best. Finally, she picks up the phone and calls the surgical pharmacy. Fortunately, the ICU PharmD is in. He straightens out her medication list and answers her questions.

So, to further understand the problems at the crux of the DDI software conundrum faced by this hypothetical young doctor, one must first look at the nature of DDIs. Of course, many DDIs are unambiguously and uniformly important. For instance, DDIs that produce drastic blood level increases in narrow therapeutic index agents (tricyclic antidepressants, lithium, digoxin, etc.) will almost invariably pose grave toxicity concerns. Additionally, DDIs that cause a significant decrease in drug concentrations lead to subtherapeutic levels and can be expected to produce therapeutic failures with potentially catastrophic outcomes. However, for the majority of DDIs, the situation is not so clear-cut. Some DDIs are situational, dependent on several factors to come into alignment. Most DDIs produce potential and/or actual suboptimal outcomes, but not frank toxicity or complete loss of efficacy. Indeed, some DDIs can be beneficial, whether by accident or the deliberate mobilization of mechanistic synergies. The question of how to address this majority of DDIs poses the first daunting challenge for the designers of DDI programs.

Secondly, most of the time, the mere fact that a DDI results from concomitant administration of two drugs does not establish that a particular DDI has any real clinical significance. Within the human species, there is great variability of both pharmacodynamic and pharmacokinetic profiles. This variability can be due to several factors including age, genetics, and pathology. This results in a spectrum of clinical responses to a given DDI, ranging from no discernible change to outright toxicity/therapeutic failure. And again, some DDIs are helpful, whether by serendipity or design. This intra-patient variability of clinical consequences arising from most DDIs makes it difficult to create a DDI program that provides consistently useful output. After all, who wants a DDI program whose most frequent result to most queries is, "anything could happen"? One might regard this as a simplistic criticism but let us examine the consequences arising from different "DDI priorities."

Intuitively, to avoid the unhelpful "anything could happen" message, the designers and programmers might design a DDI program that prioritizes probable events and de-emphasizes the merely possible. In epidemiologic language, this involves increasing *specificity* at the cost of *sensitivity*. The fewer false alarms, the more missed important interactions. While many practitioners might regard such a lack of "false alarm" alerts in the program as "user-friendly," this is small consolation to the persons who avoidably suffer from consequences of predictable and preventable DDIs that are missed by this program.

On the other hand, programs and software can be made more sensitive, to greatly minimize the risk of ever missing an important DDI. However, the price now paid is lack of specificity. In other words, the more sensitive the program, the more trivial and even frankly irrelevant "false alarm" alerts.

As noted in the papers cited above, the false alarm phenomenon is one of the biggest issues faced when using a DDI software program. An ongoing series of false and nuisance alarms caused by overly sensitive DDI programs can and will lead to "alert

fatigue." The human factors consequences of false alarms and alert fatigue are well-recognized and have been quantified. For example, it has been determined that people have a tendency to "probability match" their responses to the perceived value to the alert. That is, alerts that are 'false alarms" 90% of the time will be ignored 90% of the time.[4] More fundamentally, technologies like DDI programs act like a member of the medical team—they can provide valuable information that is useful, or they can become a burden on the team by not contributing added value. Humans have an innate and inbred ability to understand who is a good team member. People learn who to listen to on their team and who to trust. DDI programs that often "cry wolf," and who are unreliable or untrustworthy team members teach people to develop feelings of frustration and dislike, and to mistrust the program itself.

Another problem with computerized DDI programs arises due to certain inherent structural shortcomings that decrease the effectiveness of the programs. It is becoming clear that DDI databases need to take into account more patient-specific information.[5] However, most programs have not progressed to this extent; they can't supply the critical weighing of mitigating and/or exacerbating patient factors that are essential for sound clinical decision making. More simply put, clinical context is everything for both the provider and the patient, and the programs aren't very good at that. The programs don't know you, they don't know what you consider obvious, and they don't know what you would find usefully informative. Similarly, they don't know your patient. DDI programs don't "understand" the patient and context in which you operate. Few programs consider the individualized characteristics of a patient when generating warnings. As examples, hypertension as a side effect may be much more dangerous to a 92-year-old with diabetes than a healthy 27-year-old, but few DDI programs change the severity rating of a side-effect based on patient characteristics like age. The threshold for accepting risk for a given drug-drug interaction may be different if the drug therapy is contemplated for a patient with difficult to manage pain in the clinical setting of significant psychiatric disease. And of course, at this time, most DDI programs do not take into account whether a patient is a poor metabolizer at the CYP2D6 enzyme. This leads to information that is not properly prioritized, and further increases the difficulties of an efficient working relationship with a DDI program.

Interaction with DDI programs can also be a problem. On handheld devices, the process of inputting drugs into the DDI program can be inelegant, tedious, or even frustrating. For a clinician working with a DDI program imbedded in a patient's records, it can be difficult and slow for a clinician to make her way through her chart tasks in the face of repeated warnings that may be technically true, but have limited clinical relevance.

Lastly, it's not good to be too dependent on technology. Give a man a fish and you feed him for the day. Teach him to fish and you feed him for a lifetime (as well as

getting the whole weekend to yourself). DDI programs "give you a fish" by providing a list of interactions. Even if they do it correctly and meaningfully (which we know they don't), this teaches you primarily one thing: to depend on DDI programs. Learning the fundamentals of DDIs can "teach you to fish," so that you can work with confidence even when the technology is not available. Learning about DDIs can free you from depending on the program, and help you work more with patients, not computer programs.

What does the future hold for DDI software programs? The issues described above are still prevalent and the clinician must remain ever-vigilant. One possible solution is to implement more nuance and gradation into DDI programs rather than the binary choice of expressing or suppressing a given DDI. However, even simple attempts in software modification need to be done with caution, since interactions that cause patient harm may be suppressed.[6] Some programs employ a graded alert system that shows the severity of the interaction or probability of an alert's validity (red-yellow-green light symbols and other such maneuvers). However, these programs require cognitive burden on the provider. One can no longer rely on the program to provide simple "safe" vs. "unsafe" output and be guided by such unambiguous determinations. But most programs have not progressed to this extent; they can't supply the critical weighing of mitigating and/or exacerbating patient factors that are essential for sound clinical decision making. The genetic revolution has led to the new paradigm of "individualized medicine" in patient care. True individualization in therapy however, will occur only when genetics are fully integrated with all the factors, like active pathology, that currently cause variability, including DDIs. Unfortunately, we are still a long distance from that goal.

We feel the best approach to the current state of drug event and drug interaction software is to consider that acquiring fluency about drug–drug interactions is like urgently needing to learn a second language because one finds oneself suddenly living in an increasingly bilingual world. It is far better to immerse oneself in the culture of France in order to learn to speak French than it is to try to learn the language by having conversations in French that are hampered by laboriously looking up each word, one at a time. This book is designed to be a critical tool in your DDI "language immersion" process.

In summary, for better or worse, our best defense against the silent epidemic of DDIs is a well-trained, aware, and conscientious clinician who devotes specific attention to the issue of DDIs on behalf of every single patient they treat, and general attention to the subject at large. So review the vignettes, scan the tables, immerse yourself in the **Fatal Forty**, and ownership of this domain will come your way. Your patients may never know the difference, but your thanks will come in the form of decreased morbidity and mortality, and improved outcomes as well.

Take-Home Points

- Software drug–drug interaction programs are generally a necessary but not sufficient component in the mastery of DDIs.
- The sensitivity and specificity of the commercial and chart DDI software programs are often inversely proportional.
- Clinicians using these programs must be aware of, and guard against, alert fatigue.
- The editors recommend that you use commercial DDI programs much as you would use a foreign language dictionary—as a reference source, but not the sole resource for living in a foreign country. In other words, take time to actually learn and work towards fluency in the DDI language!

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