The Institute for Safe Medication Practices Canada (ISMP Canada) is an independent national not-for-profit agency established for the collection and analysis of medication error reports and the development of recommendations for the enhancement of patient safety.

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Aggregate Analysis of Medication Incidents Involving Drug Interactions

Drug interactions are preventable adverse drug events that can lead to increased morbidity and mortality, as well as additional costs to the healthcare system.[1,2] A drug interaction may occur not only between 2 or more drugs (drug–drug interaction), but also between a drug and a food or nutrient (drug–food or drug–nutrient interaction). A drug–drug interaction leads to a change in pharmacologic or clinical response of the drugs involved, such as a reduction in efficacy or an increase in toxicity, relative to the anticipated effect of each drug administered alone. Similarly, a drug–food or drug–nutrient interaction involves a nutrient or food changing the pharmacologic or clinical effects of a drug. The risk of drug interactions rises with the increasing complexity of drug regimens required to treat multiple medical conditions.

Once specific drug interactions have been established and can be identified through drug information resources (e.g., pharmacy computer systems, product monographs, or drug interaction databases), they are considered preventable. Understanding the reasons why patients continue to be exposed to these interactions, despite the availability of pertinent information, is a key step in preventing these types of medication incidents. This bulletin is intended to help identify system-based weaknesses that contribute to drug interaction incidents.

Background and Overview of Findings

Information was extracted from voluntary reports submitted to ISMP Canada's medication incident database over a period of more than 10 years (August 1, 2000, and March 25, 2011). The analysis included all reports submitted with an incident type of "Monitoring Problem – Drug–Drug Interaction" or "Monitoring Problem – Drug–Food/Nutrient Interaction" and submitted from a "hospital" care setting.

Of the 46,145 incident reports originating from hospitals, only 32 (0.07%) specified that the incident type involved a drug interaction. Of these 32 incidents, 4 (12%) resulted in patient harm or death. A total of 41 medications were associated with the 32 incident reports, but just 3 of these drugs were associated with more than half of the reported incidents: phenytoin (12 incidents), heparin (6 incidents), and enoxaparin (3 incidents).

Findings of Qualitative Analysis

The most remarkable finding from the qualitative analysis was that the majority of these interaction incidents occurred in situations where a computerized drug interaction check was available. However, in each case, the computerized check was bypassed, was overridden, or was not comprehensive. More detail about each of these 3 themes, including incident examples, is provided below.

Theme 1: Bypass of Computerized Drug Interaction Check

Incident examples:

- Staff in a hospital emergency department gave a "starter" medication kit for HIV post-exposure prophylaxis (PEP) containing the combination drugs Kaletra (lopinavir and ritonavir) and Combivir (zidovudine and lamivudine) to a patient. The patient was already taking several medications, including transdermal fentanyl. About 4 days after initiation of the PEP therapy, the patient was noted to be very drowsy and needed to be wakened frequently. Later that evening, the patient was found unresponsive, and resuscitation attempts were unsuccessful. The cause of death was determined to be toxic effects of fentanyl due to an interaction with Kaletra. This example was described in a previous Safety Bulletin.[3]

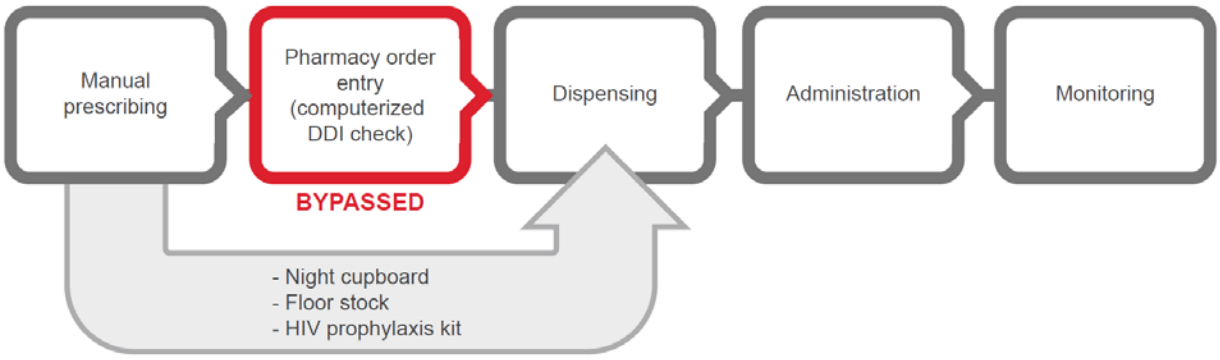

Figure 1: Illustration of a system design that allows bypass of computerized check of drug–drug interaction (DDI).

- A patient was taking multiple antibiotics, including moxifloxacin, for a bone infection. The patient was assessed by a dietitian, who suggested starting a magnesium supplement. The physician authorized the order for magnesium, which was transcribed into the medication administration record. The magnesium supplement was administered to the patient for 4 days. However, magnesium binds to moxifloxacin, and this interaction reduces the drug's effectiveness. The interaction was identified by a care team member, and the magnesium was subsequently discontinued.

Comments: The aggregate incident analysis revealed a number of medication systems that bypass computerized drug–drug interaction checks, specifically floor stock, night cupboard, and "predispensed" HIV PEP kits. These systems and associated processes are typically established to enable quick access to essential medications in situations where rapid initiation of drug therapy may be required. However, as illustrated in Figure 1, if such systems rely on manual prescribing, the processes may bypass the computerized drug–drug interaction checks that usually occur through pharmacy order entry systems.

Theme 2: Override of Drug–Drug Interaction Alerts

Incident example:

- Intravenous (IV) administration of heparin was started in the emergency department for a patient who was taking warfarin at home (with international normalized ratio [INR] 2.2). An order for enoxaparin was also initiated. The patient was transferred to the cardiac care unit, where the orders were continued. A nurse raised concerns regarding duplicate anticoagulant therapy.

Comments: It is well known that many alerts occurring during order entry are overridden, for various reasons, including "alert fatigue" related to poor specificity of the alerts (e.g., too many clinically irrelevant alerts) and lack of recognition of their importance.[4,5] The aggregate analysis identified several incidents in which drug interaction alerts for common duplicate therapies were overridden. For example, in some cases, multiple anticoagulants were inadvertently prescribed and administered, leading to an unnecessary increase in the risk of bleeding. In the setting of anticoagulant therapy, one of the potential contributing factors is that an alert will be triggered if a patient requires overlapping therapy (e.g., when warfarin therapy is started, heparin therapy is continued until the INR reaches the therapeutic range). Deliberate overlap in therapy is common practice, and the associated alerts may "desensitize" practitioners to *all* alerts for duplicate anticoagulant therapy. Although in this analysis most of the reported override-related incidents involved a duplicate alert for anticoagulants, this situation may also occur with other classes of medications, such as opioid analgesics and psychotropic medications.

Theme 3: Drug Interactions Not Included in Computerized Drug–Drug Interaction Checking Systems

Incident examples:

- Ciprofloxacin IV was ordered, and the first dose was admixed in a minibag and administered via secondary infusion. The next intermittent medication scheduled for administration was clindamycin IV. The empty minibag that had contained the ciprofloxacin was removed, and the minibag containing clindamycin was initiated through the same secondary line. These two medications are incompatible and will precipitate if mixed. In the reported incident, precipitate was found in the IV tubing after the clindamycin infusion was completed.
- Phenytoin admixed in a minibag was "piggybacked" into an IV line running dextrose 5% in water and sodium chloride 0.9%. However, phenytoin can only be diluted in, and administered with, sodium chloride solution (and a micron filter must be used). The patient later experienced seizures, which were reportedly attributed to the reduced dose of phenytoin administered because of the interaction between phenytoin and dextrose.

Comments: One type of drug interaction that may not be captured by computerized systems involves the incompatibility of drugs administered intravenously. These IV incompatibility interactions occur during the medication administration process and typically involve 2 medications mixed in the same IV bag or IV line or a medication and its vehicle. IV incompatibility interactions may result in precipitation and/or inactivation of a drug, which could lead to serious consequences.[6] It is well recognized that IV incompatibility interactions are often not included in computerized drug–drug interaction databases. Compatibility charts have therefore been developed, and the information is often also included in the IV manuals made available to front-line staff to guide practice. Manual checks based on compatibility charts and manuals must be performed at the point of administration and are prone to human error.

Recommendations and Conclusions

1. An electronic check for drug interactions is an important safeguard. For patients who require new medications, the potential for drug interactions should be evaluated with an electronic medication information database (e.g., a pharmacy information system or an online database such as Micromedex[7]). Whenever possible, the evaluation should be performed before the new medications are administered or as soon as possible after the first dose (in emergent situations).
2. Electronic order entry systems require continuous quality improvement to minimize the potential for "alert fatigue" with high-alert drugs.

3. In health centres without access to an on-site or on-call pharmacist, a consultation service should be arranged with a local community pharmacy or other drug information source.
4. Ideally, drug interaction databases should identify incompatibility issues involving IV therapy, and such information should be available and accessible to front-line staff.

Drug interactions can lead to significant patient harm but are largely preventable.[1] Recognition and detection of drug interactions by healthcare practitioners should not rely on manual checks, as studies have shown that healthcare practitioners have limited ability to consistently identify drug interactions.[4,5,8] In particular, the continuous stream of new information being added to the already vast number of documented drug interactions makes it virtually impossible for healthcare practitioners to maintain their knowledge base and identify all possible drug interactions purely on the basis of memory.[1]

The use of computerized systems for detecting drug interactions reduces overreliance on human memory to detect drug interactions. Nonetheless, opportunities exist to improve these databases. One study found that such systems may fail to detect up to a third of clinically important drug–drug interactions while alerting pharmacists to trivial issues.[9] "Alert fatigue" is one of the factors that researchers from the Institute for Clinical Evaluative Sciences have cited as a reason that drug interactions slip through.[1] The authors indicated that many hospital admissions could be avoided if certain important interactions were identified and an appropriate course of action was followed (e.g., use of therapeutic alternatives, additional monitoring).[1]

Although far from perfect, a computerized drug interaction checking system is still a key component in screening for and avoiding significant drug interactions.[1,5,8] The impact of such systems is optimized when they are used with improved information systems.[1,5] This aggregate analysis has determined that processes bypassing computerized systems, as well as certain deficits of computerized systems (e.g., lack of completeness, lack of specificity), may contribute to medication incidents.

Health service organizations, including community pharmacies, are encouraged to proactively assess their own drug interaction and monitoring processes to identify improvement opportunities to prevent significant drug interactions.

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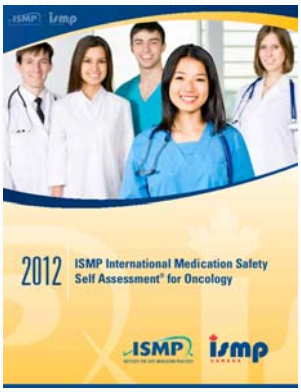
Drug Shortages and Framework for Resource Allocation

An ethical framework intended to provide high-level guidance for ethical decision-making and deliberation within and across health sectors and health institutions, as well as among healthcare professionals, in response to the current drug shortage was recently released by the Ontario Ministry of Health and Long-Term Care. Development of the framework was a collaborative effort involving multiple experts and stakeholders, including the University of Toronto Joint Centre for Bioethics. The framework is intended to guide (i) the redistribution of drug supplies across the province on the basis of need and (ii) service modification in the event of drug shortages affecting service delivery.

The full document, entitled *Ethical Framework for Resource Allocation During the Drug Supply Shortage*, is available from http://www.health.gov.on.ca/en/pro/programs/drugs/supply/docs/ethical_framework.pdf

Risk Assessment Program for Oncology Now Available



The Institute for Safe Medication Practices (ISMP US), together with ISMP Canada and the International Society of Oncology Pharmacy Practitioners, has launched the "2012 ISMP International Medication Safety Self Assessment for Oncology".

This program will assist and guide oncology practitioners working in hospitals, ambulatory care centres, and office practice settings throughout the world in identifying opportunities to improve their oncology medication-use systems. The self-assessment was developed by an international interdisciplinary panel of experts.

Canadian oncology practitioners are encouraged to participate in an international project to assess the current status of safe medication practices in the oncology setting. The program can be accessed from https://mssa.ismp-canada.org/oncology. Data can be submitted online, until **June 29, 2012,** after which time a comparative analysis of internationally submitted data will be undertaken.

For more information, please contact ISMP Canada by email, mssa@ismp-canada.org, or by telephone, 1-866-544-7672.

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