Safety Alerts as Drivers
for Pharmaceutical Opinion Program:

A Pilot Study to Reduce Potential Hospitalizations due to Preventable Drug-Drug Interactions

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Institute for Safe Medication Practices Canada
L'Institut pour l'utilisation sécuritaire des médicaments du Canada

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Drug Drug Interactions Pharmaceutical Opinion

Safety Alerts as Drivers for the Pharmaceutical Opinion Program:

A Pilot Study to Reduce Potential Hospitalizations due to Preventable Drug-drug Interactions

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Background

Drug-drug interactions (DDIs) represent a potentially serious problem that can result in adverse drug events (ADEs). Pharmacists are uniquely positioned to prevent ADEs by intervening in DDIs. Unfortunately, tertiary drug information resources are often limited in their ability to capture novel, evidence-based DDIs associated with an increased risk of hospitalization; additionally, these drug information resources often contribute to alert fatigue and desensitization among pharmacists due to an overload of DDI alerts, many of which may be clinically insignificant and not rooted in high-quality evidence.

The rationale for integrating evidence-based DDIs into pharmacy practice was to raise awareness about clinically significant DDIs associated with a potential increased risk of hospitalization. Notably, the DDIs targeted in this study (Table 1) were not consistently documented in tertiary drug information resources (Table 2), and formed the basis of an ISMP Canada Safety Alert, which supports the ongoing efforts of the pharmacy profession in proactively contributing to medication safety using evidence-based information.

Objectives

1. Reduce the occurrence of DDIs associated with a potential increased risk of hospitalization, as supported by pharmacoepidemiologic evidence.
2. Offer an educational tool to pharmacists via the Safety Alert to supplement existing tertiary drug information resources or point-of-care clinical decision support systems.
3. Motivate pharmacists to integrate cognitive services into workflow by capitalizing on the reimbursement opportunities offered by the Pharmaceutical Opinion Program (http://www.health.gov.on.ca/en/pro/programs/drugs/pharmaopinion/).

Methods

Participating pharmacists were recruited via the Ontario College of Pharmacists' register, where pharmacist members provide consent to be contacted for research purposes during their annual membership renewal.

The primary study intervention was the dissemination of the ISMP Canada Safety Alert (http://www.ismp-canada.org/download/PharmacyConnection/2013SafetyAlerts-PreventableDrug-DrugInteractions.pdf) that highlighted 13 evidence-based DDIs (Table 1) to participating pharmacies. Pharmacists reviewed this Safety Alert to allow for the recognition of the cited DDIs as they were encountered in practice, such as in the course of dispensing medications or conducting medication reviews; once identified, these DDIs were communicated to the prescriber through a documented pharmaceutical opinion.

Quantitative data was collected monthly, in the form of the number of pharmaceutical opinion claims to the Ontario Ministry of Health and Long-term Care (with prescriber responses), while qualitative data was obtained through three separate focus group sessions with study participants.

The impact of the Safety Alert in driving pharmacists' clinical interventions was measured by the number of pharmaceutical opinion claims submitted by the participating pharmacies during the six-month post-intervention period; particularly those related to the 13 evidence-based DDIs being studied (Table 1). Baseline pharmaceutical opinion data from six months prior to the intervention (i.e. the pre-intervention period) was also collected from participants.

The clinical and economic value of pharmacists' clinical interventions in preventing potential hospitalizations (associated with the 13 evidence-based DDIs) was estimated and extrapolated from the literature.

Results

Participants

In total, 66 pharmacies enrolled at study initiation, defined as having submitted their consent form to participate. During the study, 31 pharmacies withdrew or were lost to follow-up. By study conclusion, 35 pharmacies had participated in the entire six-month post-intervention period.

Quantitative

The total number of pharmaceutical opinion claims submitted by the 35 pharmacies in the six-month pre- and post-intervention periods was 2845 and 2399, respectively (Figure 1). Although this difference was not statistically significant ($p = 0.20$), the 18 pharmacies with a net increase in pharmaceutical opinions did exceed the 13 pharmacies with a net decrease.

During the post-intervention period, the 35 pharmacies submitted 230 pharmaceutical opinions regarding DDIs, 67 of which were related to the 13 evidence-based DDIs

outlined in the Safety Alert. These 67 interventions can be estimated and extrapolated to a theoretical cost avoidance of $73,184 to the health care system from potentially averted hospitalizations (Table 3).

Qualitative

The three focus group sessions generated lively discussions pertaining to several aspects of the study, including the feasibility of implementing the Pharmaceutical Opinion Program into workflow, challenges in the application of the study into practice, and collaboration with prescribers.

Overall, feedback from the focus groups affirmed the value of the Safety Alert, as it was a refresher and reminder of *clinically significant* DDIs, which was helpful in coping with alert fatigue due to numerous, automatic DDI warnings from pharmacy software and point-of-care clinical decision support systems. The Safety Alert also enabled pharmacists to acquire new information or reaffirm existing knowledge of the DDIs; the evidentiary support also empowered pharmacists to intervene with prescribers. Opportunities for study improvement and expansion to other provinces were also discussed.

Limitations

According to Kwong et al. (2009), prescriptions for respiratory antibiotics followed a narrow bell-curve distribution, reaching the highest rate in February, and the lowest in July. The six-month pre- and post-intervention periods did not align with this year-long antibiotic trend, as the usual high point in antibiotic prescribing patterns was captured in the pre-intervention period, and the low was captured in the post-intervention period. Subsequently, the 13 evidence-based, antibiotic-related DDIs in our study may not have been as prominent in the post-intervention as they were in the pre-intervention period. Extending the study to a 12-month pre- and post-intervention periods may be a more fair approach to determine the statistical significance, if any, with respect to the number of pharmaceutical opinions (or interventions) made by the pharmacists as a result of the Safety Alert.

The 13 DDIs in this study included a few chronic medications and antibiotics that are no longer commonly prescribed in practice due to emerging evidence for better alternatives. Thus, targeting DDIs involving commonly prescribed medications may have led to more clinical interventions (and subsequently higher potential cost avoidance) initiated by the participating pharmacists.

Conclusion

This project attempted to advance the profession by facilitating opportunities for pharmacists to capitalize on the Pharmaceutical Opinion Program through their clinical

knowledge of evidence-based DDIs. It is an innovative patient care strategy through the integration of patient safety (via the Safety Alert to raise awareness of DDIs with a potential increased risk of hospitalization), cognitive services (via intervention with the prescriber to prevent clinically significant DDIs), and business opportunities (via reimbursement of professional services by the Pharmaceutical Opinion Program) (Figure 2).

Reference

Kwong, J.C., Maaten, S., Upshur, R.E.G., Patrick, D.M., Marra, F. (2009). The effect of universal influenza immunization on antibiotic prescriptions: an ecological study. *Clin Infect Dis, 49*(5), 750-6.

Table 1. Drug-drug interactions with a potential increased risk of hospitalization. Evidence from primary literature of patients over 65 years old*

Drug-drug Interaction Pairs		Adverse Event or Outcome	No. of Cases Identified from ODB database	Adjusted Odds Ratio¥	Author's Comments
Chronic Medication	**Added Antibiotic**				
ACEIs / ARBs‡	TMP-SMX§	Hyperkalemia	369	6.7	*Antoniou et al. (2010)* estimated an almost **7-fold** increase in risk for hospitalization for hyperkalemia when patients on continuous treatment of ACEI or ARB were exposed to TMP-SMX within 14 days.
Calcium channel blockers	Clarithromycin	Hypotension	7100	3.70	*Wright et al. (2011)* found that patients taking a CCB were at increased risk for hospitalization for hypotension (or shock) with concurrent use of clarithromycin or erythromycin.
	Erythromycin			5.80	
Digoxin	Clarithromycin	Digoxin toxicity	1659	14.83	*Gomes et al. (2009)* estimated a **15-fold** increase in risk for hospitalization for digoxin toxicity when patients on continuous treatment with digoxin were exposed to clarithromycin within 7 days. Under similar conditions, exposure to erythromycin or azithromycin led to a **4-fold** increase in risk for hospitalization for digoxin toxicity.
	Azithromycin			3.71	
	Erythromycin			3.69	
Glyburide	TMP-SMX§	Hypoglycemia	909	5.7	*Juurlink et al. (2003)* estimated a **6-fold** increase in risk for hospitalization for hypoglycemia when patients on continuous treatment with glyburide were exposed to

Drug-drug Interaction Pairs		Adverse Event or Outcome	No. of Cases Identified from ODB database	Adjusted Odds Ratio¥	Author's Comments
Chronic Medication	**Added Antibiotic**				
					TMP-SMX within 7 days. It was estimated that at least 3.3% of these hospital admissions could have been avoided.
Phenytoin	TMP-SMX§	Phenytoin toxicity	796	2.11	*Antoniou et al. (2011)* estimated a **2-fold** increase in risk for hospitalization for phenytoin toxicity when patients on continuous treatment of phenytoin were exposed to TMP-SMX within 30 days.
Spironolactone	TMP-SMX§	Hyperkalemia	248	12.4	*Antoniou et al. (2011)* estimated a **12-fold** increase in risk for hospitalization for hyperkalemia when patients on continuous treatment of spironolactone were exposed to TMP-SMX within 14 days. Under similar conditions, exposure to nitrofurantoin led to a **2-fold** increase in risk for hospitalization for hyperkalemia.
	Nitrofurantoin			2.4	
Warfarin	TMP-SMX§	Hemorrhagic complications	2151	3.84	*Fischer et al. (2010)* estimated a **4-fold** increase in risk for hospitalization for hemorrhagic complications when patients on continuous treatment of warfarin were exposed to TMP-SMX within 14 days. Under similar conditions, exposure to ciprofloxacin led to a **2-fold** increase in risk for hospitalization for hemorrhagic complications.
	Ciprofloxacin			1.94	

Drug-drug Interaction Pairs		Adverse Event or Outcome	No. of Cases Identified from ODB database	Adjusted Odds Ratio[¥]	Author's Comments
Chronic Medication	Added Antibiotic				

[¥] Odds ratio reflects reaction within one to two weeks of exposure to antibiotic
[‡] ACEIs / ARBs = Angiotensin Converting Enzyme Inhibitors / Angiotensin Receptor Blockers
[§] TMP-SMX = Trimethoprim-Sulfamethoxazole or Cotrimoxazole

*__Note__: This information is accurate as of 2011 when the literature search and review were conducted for this study, and may not reflect the most up-to-date information / evidence and practices. This table reflects the educational material that was distributed to participating pharmacies during the study intervention in the form of a Safety Alert. The Institute for Clinical Evaluative Sciences (ICES) identified these 13 DDIs as having an increased risk of hospitalization.

Table 2. Summary of tertiary literature or drug information sources[1] on drug-drug interaction pairs with a potential increased risk of hospitalization*

Drug-drug Interaction Pairs		CPhA[2] e-therapeutics[+]/ Lexi-Interact (2012)	Drug Interaction Facts (2011) David S. Tatro (ed.)
Chronic Medication	**Antibiotic**		
ACEIs / ARBs[‡]	TMP-SMX[§]	• Risk Rating: C: Monitor therapy • Severity: Moderate • Reliability Rating: Good [Cited Antoniou et al., 2010]	No information
Calcium channel blockers	Macrolides[¥]	• Risk Rating: D: Consider therapy modification • Severity: Moderate • Reliability Rating: Good [No reference to Wright et al. (2011)]	Significance Rating: 1 (Noted as severe and well-documented interaction with concurrent use of erythromycin and diltiazem.) Based on suspected documentation (i.e. may occur; some good data; needs more study.) Significance Rating: 1 (Noted as severe and well documented with concurrent use of erythromycin and verapamil.) Based on probable documentation of case report. (i.e. very likely but not proven clinically.)
Digoxin	Macrolides[¥]	• Risk Rating: C: Monitor therapy • Severity: Moderate • Reliability Rating: Excellent [Cited Juurlink et al., 2003]	Significance Rating: 1 (Noted as severe and well-documented interaction.) Based on established documentation (i.e. proven to occur in well-controlled studies.)
Glyburide	TMP-SMX[§]	• Risk Rating: C: Monitor therapy • Severity: Moderate	No information

Drug-drug Interaction Pairs		CPhA[2] e-therapeutics[+]/ Lexi-Interact (2012)	Drug Interaction Facts (2011) David S. Tatro (ed.)
Chronic Medication	**Antibiotic**		
		• Reliability Rating: Fair [Cited Juurlink et al., 2003]	
Phenytoin	TMP-SMX[§]	• Risk Rating: C: Monitor therapy • Severity: Moderate • Reliability Rating: Excellent [No reference to Antoniou et al. (2011)]	No information
Spironolactone	TMP-SMX[§]	• Risk Rating: C: Monitor therapy • Severity: Moderate • Reliability Rating: Good [Cited Antoniou et al., 2011a]	No information
Warfarin	TMP-SMX[§]	• Risk Rating: D: Consider therapy modification • Severity: Moderate • Reliability Rating: Fair [No reference to Fischer et al. (2010)]	No information

[‡] ACEIs / ARBs = Angiotensin Converting Enzyme Inhibitors / Angiotensin Receptor Blockers
[§] TMP-SMX = Trimethoprim-Sulfamethoxazole or Cotrimoxazole
[¥] Macrolides = Azithromycin, Clarithromycin, Erythromycin

[1]The above listed tertiary literature or drug information sources are listed on *Ontario College of Pharmacists (OCP) Required Reference Guide for Pharmacies in Ontario* (Updated May 2012). Available at

Drug-drug Interaction Pairs		CPhA[2] e-therapeutics[+]/ Lexi-Interact (2012)	Drug Interaction Facts (2011) David S. Tatro (ed.)
Chronic Medication	Antibiotic		

http://www.ocpinfo.com/regulations-standards/additional-resources/reference-guide/

[2]CPhA denotes Canadian Pharmacists' Association

*__Note__: This information is accurate as of 2011 when the literature search and review were conducted, and may not reflect the most up-to-date information/evidence and practices. The above 13 DDI pairs had been identified by the Institute for Clinical Evaluative Sciences (ICES) as having an increased risk of hospitalization.

Figure 1: Total numbers of pharmaceutical opinions during the pre- and post-intervention periods

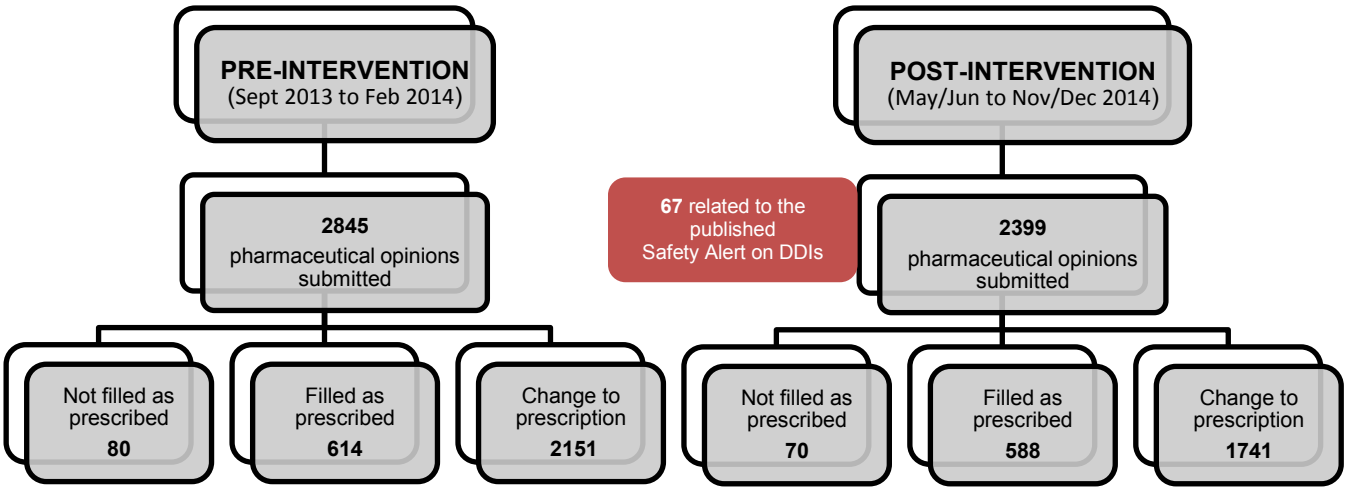

Table 3: Pharmaceutical opinions (POPs) submitted and theoretical cost avoidance results from potentially averted hospitalizations

Drug-Drug Interaction Pairs	Potential Adverse Event	Number of POPs submitted	Attributable Fraction[ɣ] (Data source for calculation)	Cost[∞] per Hospital Stay	Total Cost Avoided[§]
ACEIs[‡] + TMP-SMX*	Hyperkalemia	20	0.473 (Antoniou et al., 2010)	$6,170	$58,355
ARBs[€] + TMP-SMX*		4			$11,671
CCBs[¤] + Clarithromycin/ Erythromycin	Hypotension	12	0.004 – 0.01 (Wright et al., 2011)	$6,170	$311
Digoxin + Macrolides[¥]	Digoxin toxicity	5	0.003 – 0.03 (Gomes et al., 2009)	$13,485	$178
Glyburide + TMP-SMX*	Hypoglycemia	2	0.044 (Juurlink et al., 2003)	$10,278	$914
Phenytoin + TMP-SMX*	Phenytoin toxicity	0	0.017 (Antoniou et al., 2011)	$9,278	$0
Spironolactone + TMP-SMX*	Hyperkalemia	2	0.043 (Antoniou et al., 2011)	$6,170	$531
Spironolactone + Nitrofurantoin		1	0.016 (Antoniou et al., 2011)		$101
Warfarin + TMP-SMX*	Hemorrhagic complication	8	0.009 (Fischer et al., 2010)	$7,038	$484
Warfarin + Ciprofloxacin		13	0.007 (Fischer et al., 2010)		$639
Total	-	**67**	-	-	**$73,184**

*TMP-SMX = Trimethoprim-Sulfamethoxazole
[¥]Macrolides = Azithromycin, Clarithromycin, or Erythromycin
[‡]ACEIs = Angiotensin Converting Enzyme Inhibitors
[€]ARB = Angiotensin Receptor Blockers
[¤]CCBs = Calcium Channel Blockers

[ɣ]Derived from each DDI pair's respective literature (Table 1), using the formula: $\left[\frac{OR-1}{OR}\right] * \%\ exposed$, where *OR* is the odds ratio, and *% exposed* is the percentage of hospitalized cases of the adverse event with exposure to the DDI.

[∞]Derived from CIHI (2008). This document reported the average cost per hospital stay for common medical conditions, most of which did not include the exact definition of the DDI adverse events: hyperkalemia and hypotension were correlated to 'other symptoms and signs involving the circulatory system'; digoxin toxicity was correlated to 'other diseases of the circulatory system'; hypoglycemia was correlated to 'diabetes mellitus'; phenytoin toxicity was correlated to 'other diseases of the nervous system'; hemorrhagic complication was correlated to 'coagulation defects, purpura, and other hemorrhagic conditions'.
[§] Where there was an uncertainty in the data, the Total Cost Avoided was calculated using the most conservative figures, such that the estimates of costs avoided for each scenario would represent the minimum amount that could have been potentially saved. Final costs were rounded to the nearest dollar.

Figure 2: Integration of Patient safety, Cognitive Services, and Business Opportunities

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