

Background

- Drug-drug interactions (DDIs) can result in preventable adverse events and consumption of scarce healthcare resources.
- Pharmacists are in a unique position to prevent and monitor these adverse drug events, with the knowledge and capability to reduce DDIs.
- Tertiary drug information resources are limited in their ability to capture novel, evidence-based DDIs associated with an increased risk of hospitalization.
- Pharmacoepidemiologic evidence on drug use in the real world can be used to remedy this gap.
- The Pharmaceutical Opinion Program (POP) (<http://www.health.gov.on.ca/en/pro/programs/drugs/pharmaopinion/>) supports pharmacists for preventing drug therapy problems such as DDIs.

Table 1. Selected DDI pairs associated with an increased risk of hospitalization, as per pharmacoepidemiologic evidence from the Institute for Clinical Evaluative Sciences

Drug-Drug Interaction Pairs	Potential Adverse Event	Adjusted Odds Ratio ^a
ACEIs [‡] / ARBs [§] + TMP-SMX [*]	Hyperkalemia	6.7
CCBs [¶] + Clarithromycin	Hypotension	3.70
CCBs [¶] + Erythromycin		5.80
Digoxin + Macrolides [*]	Digoxin toxicity	C: 14.83 E: 3.69 A: 3.71
Glyburide + TMP-SMX [*]	Hypoglycemia	5.7
Phenytoin + TMP-SMX [*]	Phenytoin toxicity	2.11
Spirolactone + Nitrofurantoin	Hyperkalemia	2.4
Spirolactone + TMP-SMX [*]		12.4
Warfarin + Ciprofloxacin	Hemorrhagic complications	1.94
Warfarin + TMP-SMX [*]		3.84

^{*}TMP-SMX = Trimethoprim-Sulfamethoxazole
[‡]Macrolides = Clarithromycin [C], Erythromycin [E], or Azithromycin [A]
[‡]ACEIs = Angiotensin Converting Enzyme Inhibitors
[§]ARBs = Angiotensin Receptor Blockers
[¶]CCBs = Calcium Channel Blockers
^aAdjusted odds ratio based on hospitalization within 1 to 2 weeks of exposure to antibiotic

Objectives

- Reduce the occurrence of DDIs associated with a potential increased risk of hospitalization, as supported by pharmacoepidemiologic evidence (Table 1).
- Offer an educational tool to pharmacists via the Safety Alert to supplement existing tertiary drug information resources.
- Motivate pharmacists to integrate cognitive services into workflow by capitalizing on the reimbursement opportunities offered by the POP.

Methods

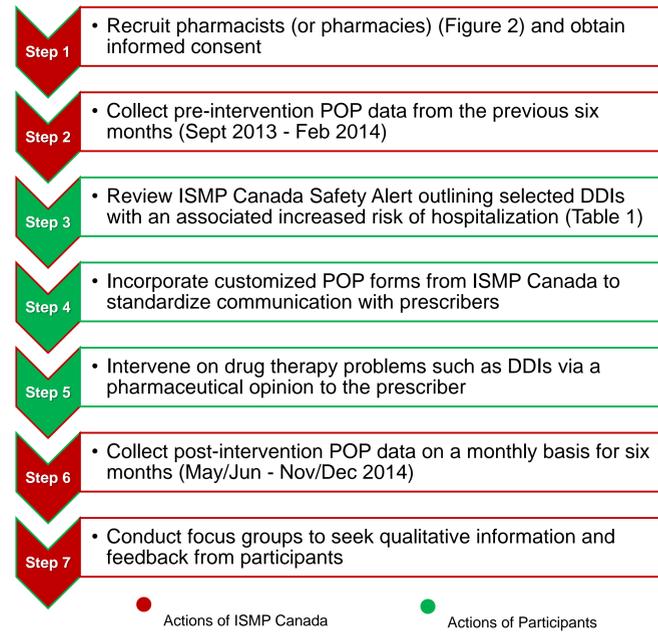


Figure 1. Overview of the steps in this non-randomized, pre-post intervention study

The two main study interventions were:

- The ISMP Canada Safety Alert outlining selected DDIs with an associated increased risk of hospitalization, as an education tool for pharmacists (<http://www.ismp-canada.org/download/PharmacyConnection/2013SafetyAlerts-PreventableDrug-DrugInteractions.pdf>).
- The customized POP forms (i.e. cover letter and pharmaceutical opinion) as a standardization tool for pharmacists' communication with prescribers.

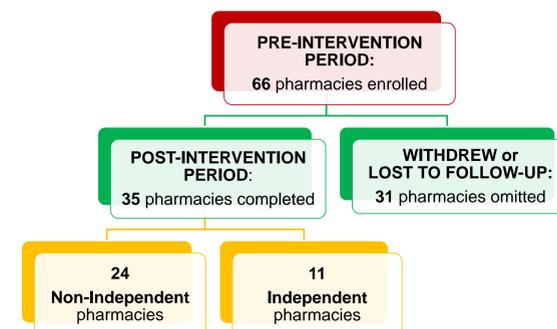


Figure 2. Study flow diagram and breakdown of participating pharmacies into non-independent (i.e. franchise, banner, and chain) and independent pharmacies

Results

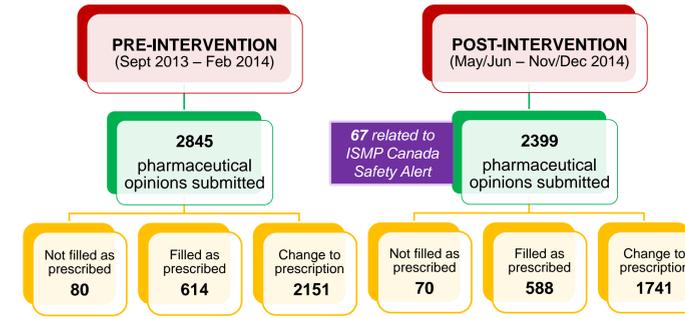


Figure 3. Total number of pharmaceutical opinion submissions pre- and post-intervention, broken down by prescriber response. Although there was an overall decrease, this difference was not statistically significant ($p = 0.204$).

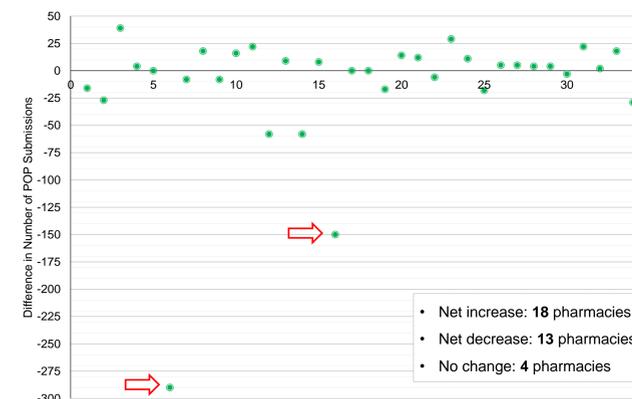


Figure 4. The difference in total number of pharmaceutical opinion submissions pre- and post-intervention per pharmacy, highlighting two outliers. The 18 pharmacies with a net increase in POP submissions exceeded the 13 pharmacies with a net decrease.

Table 2. Impact of the ISMP Canada Safety Alert on specific DDI POP submissions, and the resultant theoretical cost avoidance from 67 potentially averted hospitalizations

Drug-Drug Interaction Pairs	Potential Adverse Event	Number of POPs	Total Cost Averted ^a
ACEIs [‡] + TMP-SMX [*]	Hyperkalemia	20	\$58,355
ARBs [§] + TMP-SMX [*]		4	\$11,671
CCBs [¶] + Clarithromycin/Erythromycin	Hypotension	12	\$311
Digoxin + Macrolides [*]	Digoxin toxicity	5	\$178
Glyburide + TMP-SMX [*]	Hypoglycemia	2	\$914
Phenytoin + TMP-SMX [*]	Phenytoin toxicity	0	0
Spirolactone + Nitrofurantoin	Hyperkalemia	1	\$101
Spirolactone + TMP-SMX [*]		2	\$531
Warfarin + Ciprofloxacin	Hemorrhagic complications	13	\$639
Warfarin + TMP-SMX [*]		8	\$484
Total for study DDIs	-	67	\$73,184

^{*}TMP-SMX = Trimethoprim-Sulfamethoxazole
[‡]Macrolides = Azithromycin, Clarithromycin, or Erythromycin
[‡]ACEIs = Angiotensin Converting Enzyme Inhibitors
[§]ARBs = Angiotensin Receptor Blockers
[¶]CCBs = Calcium Channel Blockers
^aDerived from Canadian Institute for Health Information (2008). *The cost of acute care hospital stays by medical condition in Canada, 2004-2005* [Appendix C]; and the attributable fraction from each DDI study (Table 1)

Discussion

- The focus groups confirmed the value of the ISMP Canada Safety Alert, as it provided evidentiary support to empower pharmacists to communicate DDI interventions to prescribers.
- The ISMP Canada Safety Alert prompted 67 interventions on DDIs – extrapolated to a potential, theoretical cost avoidance of approximately \$16 million to the health care system if all pharmacies in Ontario participated in this study for one year.

Limitations

- Six-month pre- and post-intervention periods did not align with yearly trends in antibiotic use and staffing
 - One-year pre- and post-intervention periods would minimize confounding factors
- The targeted DDIs included medications less commonly prescribed due to emerging evidence of undesirable safety profile or more effective alternatives
 - Additional evidence-based DDIs of common medications would better impact patient health
- Total number of POP submissions was too broad to reflect impact of the Safety Alert, which targeted specific DDIs (only 3% of POP submissions)
 - Obtaining the number of POP submissions related to the Safety Alert pre- and post-intervention would permit quantitative determination of the safety alert's value
- ~50% loss to follow-up (Figure 2) reduced the clinical impact of the ISMP Canada Safety Alert
 - Provincial or national expansion would better impact patient health

Conclusion

- DDIs are pervading issues frequently faced by health care practitioners and patients, and pharmacists are most well-suited to identify and address DDIs.
- The ISMP Canada Safety Alert successfully:
 - educated pharmacists on DDIs associated with an increased risk of hospitalization;
 - encouraged pharmacists to intervene on 67 DDIs (with potential costs avoided to the healthcare system (Table 2);
 - motivated pharmacists to continue to implement the POP for reimbursement of cognitive services.