Advancing Safe Medication Practices

ismp CANADA

Drug Interaction Pairs Associated with an Increased likelihood of Hospitalization: A New Look at the Evidence

Roger Cheng, RPh, BScPhm, PharmD
Project Leader,
Institute for Safe Medication Practices Canada (ISMP Canada)

Outline

- Background
- Screening and avoidance of significant drug interactions
  - Practitioners
  - Computer systems
  - Drug interaction compendia
- Generating the evidence:
  - Recent developments
  - An example
- What can we do?
- Conclusion

Presented with support from Health Canada

Clinical Scenario

- A 46-year-old patient was provided with a "starter" medication kit for HIV post-exposure prophylaxis (PEP) by hospital emergency department
- Kit contained Kaletra® (lopinavir and ritonavir) and Combivir® (zidovudine and lamivudine)
- Patient's regular medications: venlafaxine, amitriptyline, bupropion, hormone replacement therapy, and fentanyl patch 100 mcg/h.

Presented with support from Health Canada

Clinical Scenario

- Approximately 4 days after initiation of PEP, patient noted to be very drowsy and needed to be frequently wakened
- Went to lie down and some time later that evening was found unresponsive. Resuscitation attempts were not successful.
- Based on post-mortem examination and serum drug levels, the cause of death was determined to be fentanyl toxicity due to an interaction with Kaletra®.

Drug Interaction Incident with HIV Post-exposure Prophylaxis. *ISMP Can Saf Bull* 2008; 8(3). Available at: http://www.ismp-canada.org/download/safetyBulletins/ISMPCSB2008-03HIVPEP.pdf

Presented with support from Health Canada

Drug Interaction: Introduction

- Definition:
  - A pharmacokinetic or pharmacodynamic influence of drugs on each other, which can result, beside desired effects, in reduced effectiveness or increased toxicity.
- In theory, preventable in most cases
  - Therapeutic alternatives usually exist
  - Not all drugs within a drug class are susceptible to the same drug interactions (e.g., statins)

Becker ML, Kallewaard M, Caspers PW, Schalekamp T, Stricker BH. Potential determinants of drug-drug interaction associated dispensing in community pharmacies. Drug Saf. 2005;28(5):371-8.

Shapiro LE, Shear NH. Drug-drug interactions: how scared should we be? CMAJ. 1999 Nov 16;161 (10):1266-7

Presented with support from Health Canada

Significance

From a population perspective:

- In ambulatory and outpatient settings, 9-70% of patients are exposed to drugs with a risk of drug interactions, 1-23% of these being of major relevance
- It is estimated that drug interactions cause up to 2.8% of hospital admissions
- May be especially significant for the Long Term Care population

Van Roon, EN, Flikweert S, le Comte M, et al. Clinical relevance of drug-drug interactions: a structured assessment procedure. Drug Saf 2005; 28:1131-9.

Shapiro LE, Shear NH. Drug-drug interactions: how scared should we be? CMAJ. 1999 Nov 16;161(10):1266-7.

Presented with support from Health Canada

Classification

- Pharmacokinetic vs. pharmacodynamic interactions
  - Pharmacodynamic interactions: Direct addition or antagonism of pharmacological effects
  - Pharmacokinetic interactions: One drug changes the absorption, distribution, metabolism or excretion of another drug
- Provides understanding of the mechanism, however, less helpful in practical management

Presented with support from Health Canada

Classification

- Classification according to clinical significance
  - Various severity rating scales: e.g., major, moderate, minor, none, not specified
- ORCA: **O**pe**R**ational **C**lassific**A**tion of Drug Interactions
  - Oriented towards clinical management: contraindicated, provisionally contraindicated, conditional, minimal risk, no interaction

Hansten PD, Horn JR, Hazlet TK. ORCA: OpeRational ClassificAtion of drug interactions. J Am Pharm Assoc (Wash). 2001 Mar-Apr;41(2):161-5.

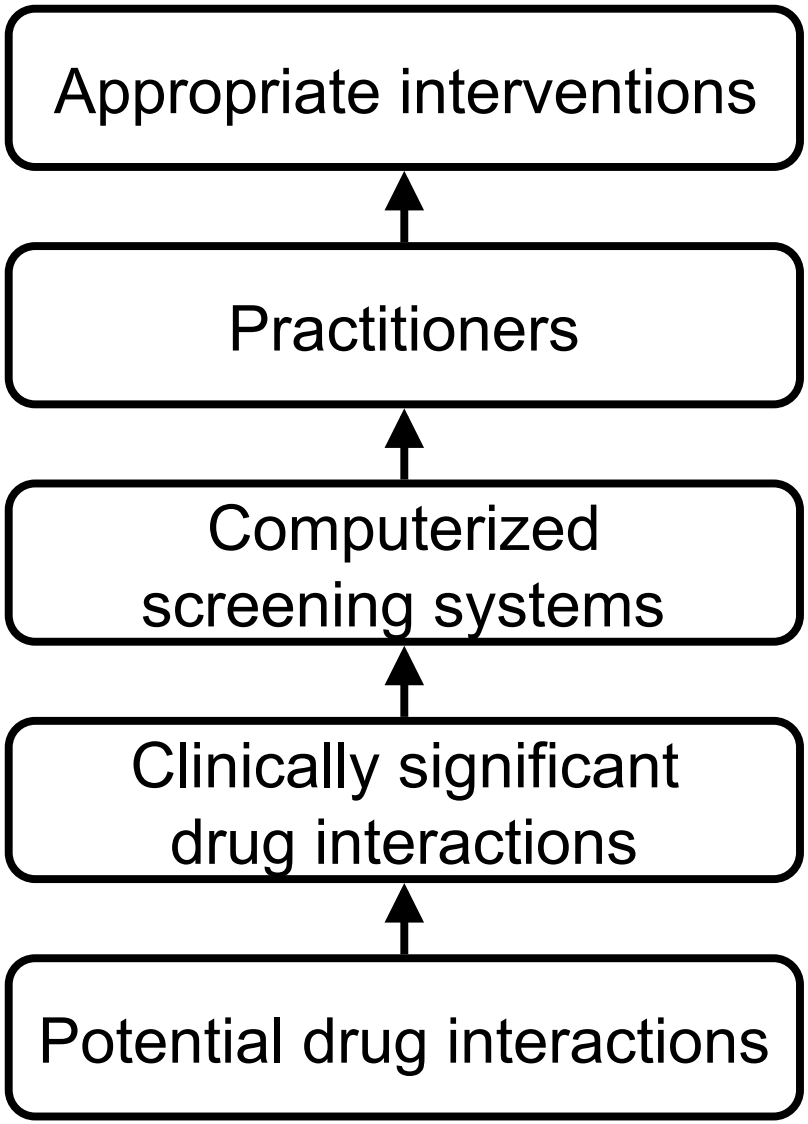
Presented with support from Health Canada

Clinical Literature

- More than 15,000 journal articles on drug interactions published
- Overwhelming majority are *in vitro* studies, pharmacokinetic studies or case reports
- Determination of clinical significance of a particular interaction is difficult
  - Estimates of significance are projections based on the clinical literature

Presented with support from Health Canada

Screening and Avoidance



Screening and Avoidance: Practitioners

- Studies found that clinicians (physicians, nurse practitioners and pharmacists) correctly categorized only 44% - 66% of drug interactions

Glassman PA, Simon B, Belperio P, Lanto A. Improving recognition of drug interactions: benefits and barriers to using automated drug alerts. Med Care. 2002 Dec;40(12):1161-71.

Weideman RA, Bernstein IH, McKinney WP. Pharmacist recognition of potential drug interactions. Am J Health Syst Pharm. 1999 Aug 1;56(15):1524-9.

Presented with support from Health Canada

Screening and Avoidance: Computer Systems

- A study found that only 18 (28%) of 64 pharmacies detected all the clinically significant drug interactions tested
- Another similar study examined 9 computer drug interaction software programs (in 516 community pharmacies)
  - Failed to detect clinically relevant drug interactions one-third of the time

Saverno KR, Hines LE, Warholak TL, Grizzle AJ, Babits L, Clark C, Taylor AM, Malone DC. Ability of pharmacy clinical decision-support software to alert users about clinically important drug-drug interactions. J Am Med Inform Assoc. 2011 Jan 1;18(1):32-7.

Hazlet TK, Lee TA, Hansten PD, Horn JR. Performance of community pharmacy drug interaction software. J Am Pharm Assoc (Wash). 2001 Mar-Apr;41(2):200-4.

Presented with support from Health Canada

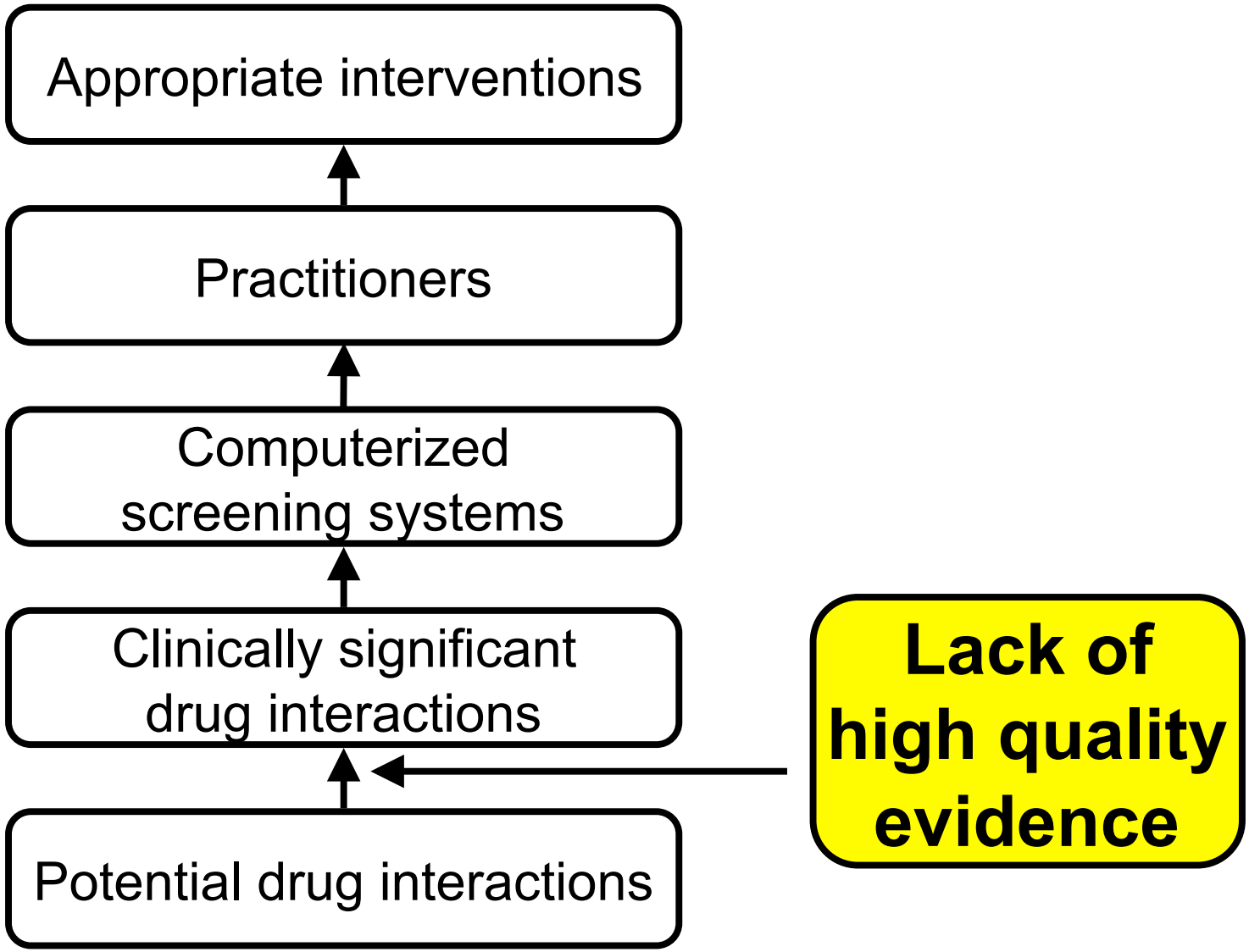
Drug Interaction Compendia

- Accurate identification of clinically significant drug interactions depends on the quality of its content
- An assessment of four leading international interaction compendia found that of those classified as major in any one compendium, between 14% and 44% were not listed in the other compendia
- Conclusion: *"There is a lack of consistency in the inclusion and grading of drug-drug interactions of major significance…across the four drug compendia examined."*

Vitry AI. Comparative assessment of four drug interaction compendia. Br J Clin Pharmacol. 2007 Jun;63(6):709-14.

Presented with support from Health Canada

Screening and Avoidance



Generating the Evidence

- Urgent need for reliable evidence regarding the clinical significance of specific drug interactions
- Randomized controlled trials??
- Recent developments:
  - Utilization of pharmacoepidemiologic methodologies to study adverse outcomes of specific drug interactions
  - Population-based data, large numbers, relevant patient outcomes studied

New Research Example

Purpose:

"To characterize the clinical significance of this drug interaction by determining the risk of hyperkalemia after the prescription of trimethoprim-sulfamethoxazole to older patients who are being treated with either an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker."

Antoniou T, Gomes T, Juurlink DN, Loutfy MR, Glazier RH, Mamdani MM. Trimethoprim-sulfamethoxazole-induced hyperkalemia in patients receiving inhibitors of the renin-angiotensin system: a population-based study. Arch Intern Med. 2010 Jun 28;170(12):1045-9.

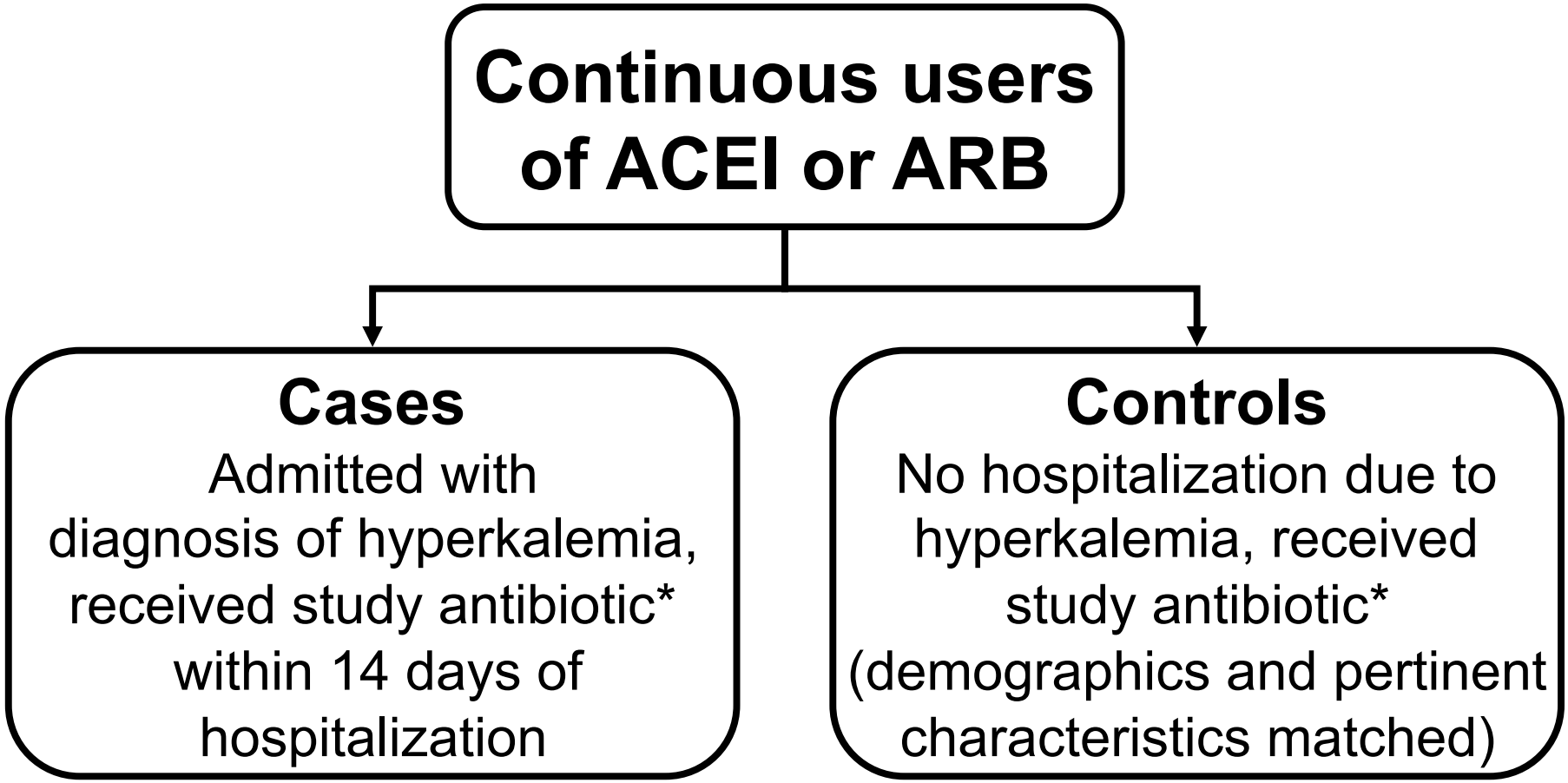
Presented with support from Health Canada

New Research – Methodology

- Population-based, retrospective, nested case-control study
- Linkage of multiple national and provincial databases
- Patient inclusion criteria:
  - 66 years or older
  - Resident of Ontario
  - Receiving continuous therapy with either an ACEI or an ARB
- Timeframe: April 1, 1994 to March 31, 2008

Presented with support from Health Canada

New Research: Methodology



*Study antibiotics included TMP-SMX, ciprofloxacin, norfloxacin, nitrofurantoin or amoxicillin (reference)

Presented with support from Health Canada

New Research - Findings

Drug	Cases	Controls	Adjust OR (95% CI)
TMP-SMX	204 (55.6%)	323 (22.8%)	**6.7 (4.5 – 10.0)**
Norfloxacin	20 (5.4%)	163 (11.5%)	0.8 (0.4 – 1.5)
Ciprofloxacin	76 (20.7%)	413 (29.1%)	1.4 (0.9 – 2.2)
Nitrofurantoin	18 (4.9%)	129 (9.1%)	1.1 (0.6 – 2.0)
Amoxicillin	49 (13.4%)	389 (27.5%)	1 (reference)

Presented with support from Health Canada

New Research: Findings

Results:

- "Cases were almost 7 times more likely than controls to have received a prescription for TMP-SMX than for amoxicillin in the 14 days preceding admission."
- "No association was found between hyperkalemia-related hospitalization and the use of any other study antibiotic."
- "Median length of hospitalization was 6 (3-13) days."

Presented with support from Health Canada

New Research: Findings

Conclusion:

- Among older patients treated with ACEIs or ARBs, the use of TMP-SMX is associated with a major increase in the risk of hyperkalemia associated hospitalization relative to other antibiotics.

Presented with support from Health Canada

Clinically Significant DDI Pairs

Drug Interaction Pairs	Reason for hospitalization
Glyburide and cotrimoxazole	Hypoglycemia
Digoxin and clarithromycin	Digoxin toxicity
ACEI and potassium sparing diuretic	Hyperkalemia
Proton pump inhibitors and clopidogrel (Post MI)	Reinfarction
Warfarin and cotrimoxazole	Hemorrhage

- Juurlink DN, Mamdani M, Kopp A, Laupacis A, Redelmeier DA. Drug-drug interactions among elderly patients hospitalized for drug toxicity. JAMA. 2003 Apr 2;289(13):1652-8.
- Fischer HD, Juurlink DN, Mamdani MM, Kopp A, Laupacis A. Hemorrhage during warfarin therapy associated with cotrimoxazole and other urinary tract anti-infective agents: a population-based study. Arch Intern Med. 2010 Apr 12;170(7):617-21.
- Juurlink DN, Gomes T, Ko DT, Szmitko PE, Austin PC, Tu JV, Henry DA, Kopp A, Mamdani MM. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. CMAJ. 2009 Mar 31;180(7):713-8.

Presented with support from Health Canada

Clinically Significant DDI Pairs

Drug Interaction Pairs	Reason for hospitalization
Lithium and ACEI or loop diuretics	Lithium toxicity
Digoxin and macrolide antibiotics	Digoxin toxicity
Warfarin and NSAIDs	Upper GI hemorrhage
Tamoxifen and paroxetine	Breast cancer treatment failure
Calcium channel blockers and macrolide antibiotics	Hypotension

- Juurlink et al. Drug-induced lithium toxicity in the elderly: a population-based study. *JAGS*. 2004; 52: 794-798.
- Gomes et al. Macrolide-induced digoxin toxicity: a population-based study. *Clin Pharmacol Ther*. 2009; 86(4): 383-386.
- Battistella et al. Risk of upper gastrointestinal hemorrhage in warfarin users treated with nonselective NSAIDs or COX-2 inhibitors. *Arch Intern Med*. 2005; 165: 189-192.
- Kelly et al., Selective serotonin reuptake inhibitors and breast cancer mortality in women receiving tamoxifen: a population based cohort study. *BMJ*. 2010; 340: c693.
- Wright et al., The risk of hypotension following co-prescription of macrolide antibiotics and calcium-channel blockers. *CMAJ*. 2011; 183(3): 303-307.

Presented with support from Health Canada

Clinically Significant DDI Pairs

Drug Interaction Pairs	Reason for hospitalization
Phenytoin and TMP-SMX	Phenytoin toxicity
Spironolactone and TMP-SMX	Hyperkalemia
Theophylline and ciprofloxacin	Theophylline toxicity
Warfarin and fluconazole	Gastrointestinal bleeding

- Antoniou et al. Trimethoprim/sulfmethoxazole-induced phenytoin toxicity in the elderly: a population based study. *Br J Clin Pharmacol*. 2011; 71(4): 544-549.
- Antoniou et al. Trimethoprim-sulfamethoxazole induced hyperkalemia in elderly patients receiving spironolactone: nested case-control study. *BMJ*. 2011; 343: d5228
- Antoniou et al. Ciprofloxacin-induced theophylline toxicity: a population study. *Eur J Clin Pharmacol*. 2011; 67: 521-526.
- Schelleman H, Bilker WB, Brensinger CM, Han X, Kimmel SE, Hennessy S. Warfarin with fluoroquinolones, sulfonamides, or azole antifungals: interactions and the risk of hospitalization for gastrointestinal bleeding. Clin Pharmacol Ther. 2008 Nov;84(5):581-8.

Presented with support from Health Canada

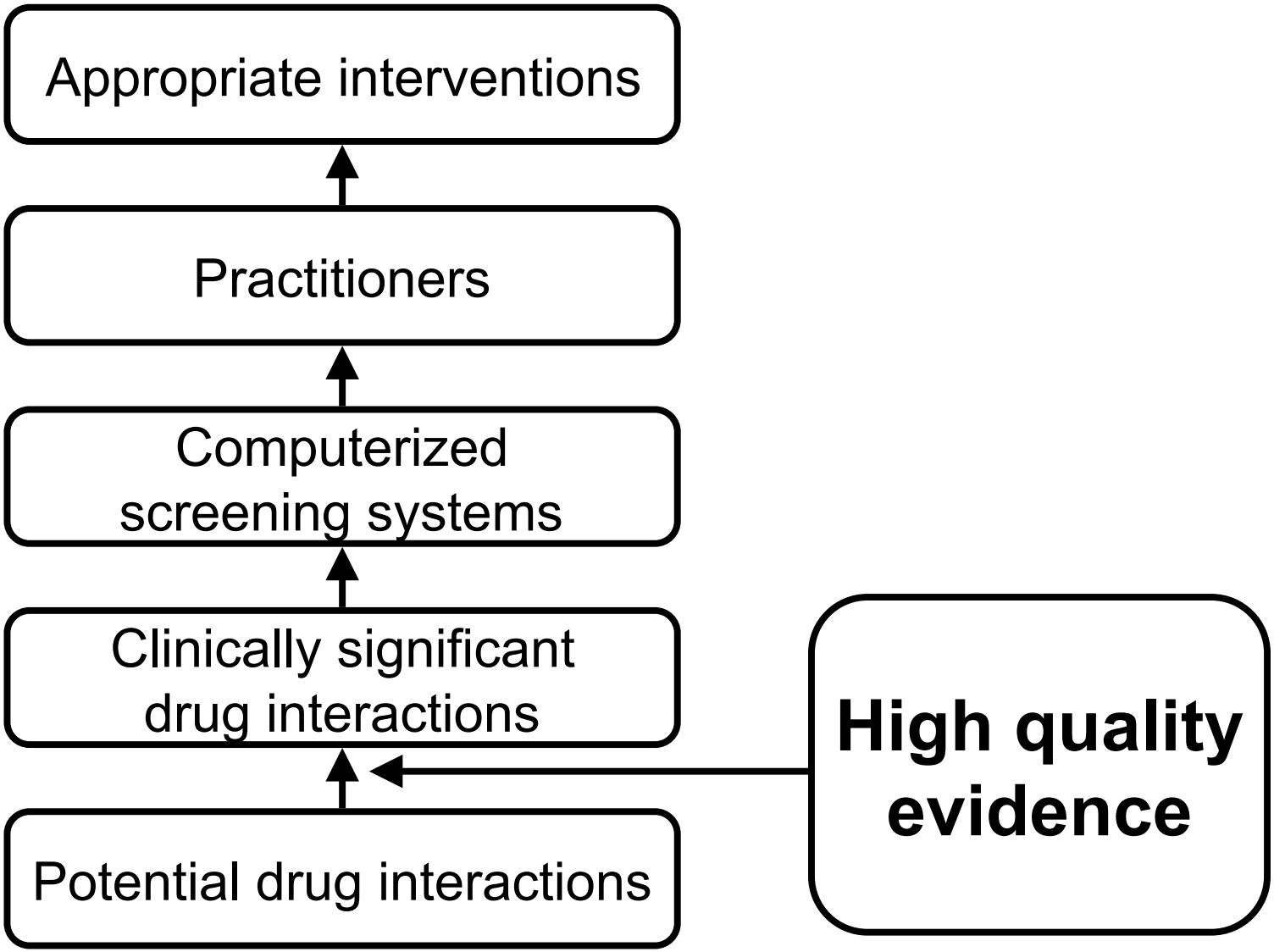
Additional Research

Other pharmacoepidemiologic studies examining specific drug interactions showing **NO increases** in hospitalization**:**
Warfarin and levofloxacin
Beta-blockers and cotrimoxazole
Digoxin and SSRIs
Warfarin and SSRIs

- Stroud LF, Mamdami MM, Kopp A, Bell CM. The safety of **levofloxacin** in elderly patients on **warfarin**. Am J Med. 2005 Dec;118(12):1417.
- Weir MA, Juurlink DN, Gomes T, Mamdani M, Hackam DG, Jain AK, Garg AX. **Beta-blockers, trimethoprim-sulfamethoxazole**, and the risk of hyperkalemia requiring hospitalization in the elderly: a nested case-control study. Clin J Am Soc Nephrol. 2010 Sep;5(9):1544-51.
- Kurdyak et al. Antidepressants, warfarin, and the risk of hemorrhage. *J Clin Psychopharmacol*. 2005; 25(6): 561-564.
- Juurlink et al. A population-based assessment of the potential interaction between serotonin-specific reuptake inhibitors and digoxin. *Br J Clin Pharmacol*. 2005; 59(1): 102-107.

Presented with support from Health Canada

Generating the Evidence



Generating the Evidence

- Limitations
  - Generalizability: Results only applicable to study population (e.g., 65 or older, community settings)
  - Critical appraisal is still required

- Status quo is unacceptable!

Presented with support from Health Canada

What can we do?

- Memorize a "short list"
  - Common "precipitants"
    - Antibiotics
    - SSRI
    - Verapamil, Diltiazem
    - Amiodarone
    - Tramadol
    - Antiretrovitals

- Juurlink, D. A Practical Approach to Drug Interaction. CSHP 2012 (Presentation)

Presented with support from Health Canada

What can we do?

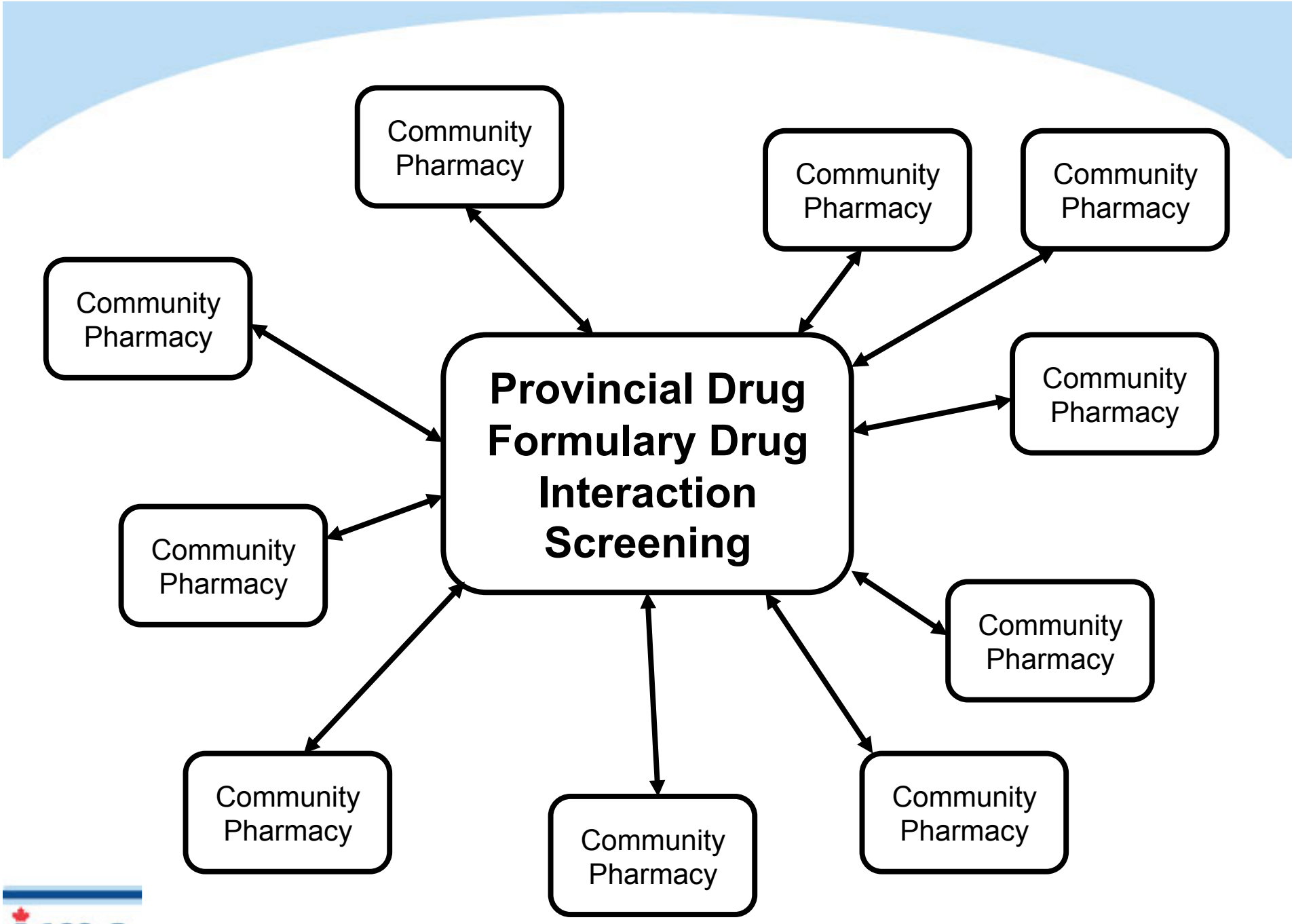
- Be alert when patients on high – risk drugs
  - Warfarin
  - Dabigatran
  - Digoxin
  - Sylfonylureas
  - Statins
  - CCB
  - Miscellaneous
    - Anticonvulsants, lithium, theophylline, immunosuppressants
- Juurlink, D. A Practical Approach to Drug Interaction. CSHP 2012 (Presentation)

Presented with support from Health Canada

What can we do?

- Community pharmacy settings
  - Unique opportunity:
    - Drug claims from all community pharmacies within a particular geographical area (e.g., province) all go through the drug benefit plan's (provincial plan or private insurance drug plans) central system
    - Ideal point for drug interaction screening and implementing appropriate interventions

Presented with support from Health Canada


Community Pharmacy
Community Pharmacy
Community Pharmacy
Community Pharmacy
Provincial Drug Formulary Drug Interaction Screening
Community Pharmacy
Community Pharmacy
Community Pharmacy
Community Pharmacy
Community Pharmacy
Community Pharmacy
Community Pharmacy

Opportunities for Collaboration

- A plan to systemically reduce hospitalizations due to drug interactions

- Collaboration among stakeholders:
  - Governments, provincial governmental and private drug plans, researchers, clinical experts, medication safety organizations

Presented with support from Health Canada

Conclusion

- Drug interactions increase hospitalizations – these hospitalizations are largely preventable
- Current systems for drug interaction screening and avoidance are suboptimal
  - One of the main reasons is the lack of high quality evidence
- Pharmacoepidemologic drug interaction studies can greatly facilitate the identification of clinically significant interactions, a fundamental step for systematic enhancement of strategies for screening and avoidance

Presented with support from Health Canada

Questions?

Roger Cheng, RPh, BScPhm, PharmD

Project Leader, ISMP Canada

rcheng@ismp-canada.org

(416) 733-3131 ext 229

Presented with support from Health Canada