Data Impact Challenge II Answer Submission

- Challenge Question: To what extent does re-prescribing and re-dispensing of culprit drugs contribute to the burden of adverse drug events presenting to Canadian hospitals?

- Team name and list of all team member names: ICES Western (Jennifer Winick-Ng, Lucie Richards, Kristin Clemens, Salimah Shariff, Blayne Welk)

Background: In the United States, 2 million patients experience serious adverse drug events (ADEs) each year, and over 100,000 hospital patients will die as a result. In-hospital ADE may be associated with permanent disability, ICU admission, and death in 20-25% of cases. The BEERs and the STOPP criteria identify medications that are inappropriate in the elderly due to a high risk of ADEs. Both of these guidelines identify neuroleptics (antipsychotic) and benzodiazepines as medications which should be discontinued after a fall in an elderly patient as a consistent association between these medications and falls has been demonstrated. Falls are extremely pertinent in the elderly as there is an estimated 50% mortality rate during the first year after a fall requiring hospitalization. These guidelines further suggest that glyburide (an antihyperglycemic medication used by diabetics) should be avoided in the elderly due to its risk of severe hypoglycemia compared with other agents. Hypoglycemia can have significant consequences including cardiac disturbance, neurological dysfunction, impaired quality of life and even death. Our objective was to use these medications and their well-recognized ADEs to answer this challenge question.

The Data and Analysis

- Data Custodian Organization(s) and data sources: Institute for Clinical Evaluative Sciences (ICES) Western

- List of Datasets Used: Ontario Drug Benefits (ODB, which has >99% accuracy for prescribed medications, and includes all medications used by Ontarians who are >65 years of age), the Canadian Institute for Health Informatics Discharge Abstract Database (CIHI-DAD) and the National Ambulatory Care Reporting System (NACRS) for inpatient and emergency room admissions in Ontario; data quality for both of these sources has been measured and is actively maintained through audit feedback systems.

- Exclusions: Prescription for the medication of interest within the prior year, the specified ADE occurred in the 90 days prior to the first prescription, or patient was a non-Ontario resident.

- Nature and Size of Cohort: This was a population-based cohort drawn from all Ontario citizens >66 years of age as of March 2015 or earlier. 1.2 million people >66 years of age received one of these prescriptions in Ontario during the study period.

- Data timeframe: January 1 2004-March 31 2015 (12 years)

Methodology: We created 3 cohorts of patients who received a new prescription for glyburide, benzodiazepines, or neuroleptics using drug identification numbers and ODB records. A total of 1,160 unique DINs which were representative of the relevant medication classes were included. We then identified patients who presented to a hospital emergency room or required hospital admission for a medication-specific ADE (hypoglycemia or fall) within 3 months of the initiation of the new prescription (using NACRS and CIHI-DAD). Hypoglycemia was defined as ICD 10 codes E15, E160, E161, E162, E1063, E1163, E1363 or E1463 (positive predictive value 94%, determined from a medical chart review which defined true hypoglycemia as a blood glucose <4 or a physician diagnosis of hypoglycemia), while falls were defined as an ICD 10 code W00-W19 (positive predictive value 91% compared to medical chart review) from the diagnosis fields in CIHI-DAD and NACRS. Our primary outcome was re-dispensing (either due to a new prescription, or refilling a standing prescription) of the same drug or drug class within 180 days of the ADE.
Results: The baseline demographic information of our cohort of 31,265 patients is shown below. All of these patients experienced the specified ADE. Means and standard deviations are reported.

<table>
<thead>
<tr>
<th></th>
<th>Glyburide (ADE=hypoglycemia)</th>
<th>Benzodiazepines (ADE=fall)</th>
<th>Neuroleptics (ADE=fall)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>1,313</td>
<td>15,793</td>
<td>14,159</td>
<td>31,265</td>
</tr>
<tr>
<td>Age (years ± standard deviation)</td>
<td>76.9 ± 7.8</td>
<td>79.0 ± 8.8</td>
<td>82.1 ± 8.1</td>
<td>80.3 ± 8.6</td>
</tr>
<tr>
<td>Female (percentage)</td>
<td>667 (50.8%)</td>
<td>10,064 (63.7%)</td>
<td>8,986 (63.5%)</td>
<td>19,717 (63.1%)</td>
</tr>
<tr>
<td>Long term care resident</td>
<td>155 (11.8%)</td>
<td>3,802 (24.1%)</td>
<td>4,790 (33.8%)</td>
<td>8,747 (28.0%)</td>
</tr>
<tr>
<td>Total number of medications</td>
<td>1.5 ± 0.9</td>
<td>1.5 ± 0.9</td>
<td>1.8 ± 1.0</td>
<td>1.6 ± 1.0</td>
</tr>
<tr>
<td>Co-prescribing</td>
<td>3,401 (21.5%)</td>
<td>5,123 (36.2%)</td>
<td></td>
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<tr>
<td></td>
<td>were also on a neuroleptic</td>
<td>were also on a benzodiazepine</td>
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Numerator and Denominator: Overall, 54.7% of patients were re-dispensed the medication within 180 days.

<table>
<thead>
<tr>
<th></th>
<th>Proportion re-dispensed medication within 180 days of an ADE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glyburide</td>
<td>500/1313 (38.1%)</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>7590/15793 (48.1%)</td>
</tr>
<tr>
<td>Neuroleptic</td>
<td>9007/14159 (63.6%)</td>
</tr>
<tr>
<td>Total</td>
<td>17097/31265 (54.7%)</td>
</tr>
</tbody>
</table>

• When looking at each of these medication groups individually, the majority of the time (>85%), patients were re-dispensed the medication within 90 days of the ADE, and most of the time (>63%) the prescription was from the same physician who initiated the prescription.

• Among the patients who were re-dispensed the medication after the initial ADE, a median of 2 glyburide prescriptions (interquartile range (IQR) 1-5), 2 benzodiazepine (IQR 1-6), and 9 (IQR 3-25) neuroleptic prescriptions were re-dispensed within 180 days.

• Among people who experienced the specified ADE, and then the drug was re-dispensed, a second ADE was experienced within 90 days by 66/500 glyburide (13.2%) users, 744/7590 (9.8%) benzodiazepine users, and 1145/9007 (12.7%) neuroleptic users.

• Additional analysis: We explored significant variations in the re-dispensing of these medications both over time, and across geographic regions in Ontario. The re-dispensing of benzodiazepines and neuroleptics both demonstrated a small but significant decline over the study period (Figure 1). There was considerable geographical variation in Ontario in terms of re-dispensing of neuroleptics and benzodiazepines (Figure 2-3). Figure 4 shows the geographic changes in re-dispensing rates of benzodiazepine and neuroleptics over time.
Figure 1. Trend over time in the re-dispensing of medications after an ADE for glyburide, benzodiazepines, and antipsychotics (neuroleptics) based on fiscal years.

$p$ values refer to the results of a Cochrane-Armitage linear trend test.
Figure 2 - Regional variation in rate of benzodiazepine re-dispensing after fall resulting in hospital encounter

Proportion of seniors (ages 66+) newly on benzodiazepine who have a fall leading to hospital encounter and are re-dispensed benzodiazepine within 6 months
By census division, Ontario

Legend
Percent represcribed
Less than 40%
40.1% - 45%
45.1% - 50%
50.1% - 55%
55.1% - 60%

Note:
Numerator = # newly on drug who have an event AND are re-dispensed drug within 6 months
Denominator = # newly on drug who have an event.

Institute for Clinical Evaluative Sciences, 2016
Data sources:
- CIHI Discharge Abstract Database
- National Ambulatory Care Reporting System
- Ontario Drug Benefit Database
- Statistics Canada geographic boundaries
Figure 3 - Regional variation in rate of neuroleptic re-dispensing after fall resulting in hospital encounter

Proportion of seniors (ages 66+) newly on a neuroleptic who have a fall leading to hospital encounter and are redispensed a neuroleptic within 6 months

By census division, Ontario

Legend
Percent re-prescribed
- Less than 55%
- 55.1% - 60%
- 60.1% - 65%
- 65.1% - 70%
- 70.1% - 75%

Note:
Numerator = # newly on drug who have an event AND are redispensed drug within 6 months
Denominator = # newly on drug who have an event.

Institute for Clinical Evaluative Sciences, 2016
Data sources:
- CIHI Discharge Abstract Database
- National Ambulatory Care Reporting System
- Ontario Drug Benefit Database
- Statistics Canada geographic boundaries
Figure 4 – Change between 2004-2015 in the regional variation in rate of neuroleptic and benzodiazepine re-dispensing after a fall resulting in hospital encounter. Please click to view (requires Acrobat 9.0 or later), or go to https://youtu.be/d0IKHuUOGJg
**Discussion:** We demonstrated a high rate of re-dispensing of high-risk medications after a specific and potentially serious ADE. This was surprising, given the known risks associated with these medications. While there was a statistically significant decrease in the re-dispensing of benzodiazepines and neuroleptics over time, the magnitude of this decrease was quite small. The geographical variation in these practise patterns in Ontario was quite striking and further exploration of correlations with specific healthcare technology, or mechanisms of communication between acute care providers and primary care teams should be explored.

- **Strengths:** We evaluated 3 separate medication classes, and found consistently high re-dispensing rates in all groups. The ADEs that we identified are potentially serious, and the discontinuation of the medications after their related ADEs are recognised as good practise by well-known medical guidelines. In order to maximise generalisability, we used a very large sample size derived from the entire population of Ontario to minimise selection bias. As requested by the challenge question, we have selected ADEs with known measurement characteristics (in this case positive predictive values, which define the probability that a person with the ICD code had the ADE; in the case of our specific ADEs the PPVs are >90%).

- **Limitations:** We were not able to use administrative data to determine how definitively the ADE was attributable to the medication, as both falls and hypoglycemia in the elderly may be multifactorial. The smaller sample size in the glyburide group limited the interpretation of some of our additional analyses, such as the trend over time. In some cases, the benefit of the medication may have outweighed the potential risk of repeat ADE, and therefore an informed decision was made to continue to medication despite the risks. Finally, our results may not be generalizable to younger patients.

- **Policy Implications:** Re-dispensing medications after an ADE could represent a failure of the physician to recognise that an ADE occurred, (and therefore they continue prescribing), or it could represent a failure of the pharmacy or patient to discontinue a prescription with refills on file. Improvements in physician awareness of the risk of falls as an ADE for benzodiazepines and neuroleptics and hypoglycemia with the use of glyburide, may explain the decrease in re-dispensing of these medications over time. As patients may simply be returning to their home medications after discharge from hospital following an ADE, funding of systems to further involve pharmacists in evaluating ADEs might be useful. If pharmacists received a notification (with a diagnosis and main reason for admission) after a hospital stay or emergency room visit of one of their patients, they could play an enhanced role in maintaining patient safety after an ADE. Further research to assess why certain geographical areas tend to perform better on this metric of re-dispensing after an ADE is indicated. This would provide important evidence as to effective interventions which could be applied across the province and validate the use of this metric as an easily applied quality of care indicator that would be applicable to the Local Health Integration Networks.
References


14. Personal communication, Dr Kristin Clemens, (based on a validation study, manuscript in preparation) February 16, 2016.

15. Personal communication, (based on a validation study, manuscript in preparation), Dr Lisa-Ann Fraser, September 4, 2015.