March 2013

Analysis in Brief

Adverse Drug Reaction–Related Hospitalizations Among Seniors, 2006 to 2011

Types of care

Introduction

Adverse drug reactions (ADRs) are defined by the World Health Organization (WHO) as adverse effects of a drug that was properly administered in the correct dose, for therapeutic or prophylactic (that is, preventive) use.[1] Previous studies have estimated that between 1% and 25% of all hospital admissions and emergency department (ED) visits are drug-related, with estimates varying by study design and data source.[2–5] ADRs have been estimated to account for up to two-thirds of drug-related hospital admissions and ED visits.[2–5]

It has been reported that up to one-quarter of patients who visit EDs due to ADRs are admitted to hospital.[4, 5] ADRs resulting in hospital admission generally represent more severe reactions and require more resources to treat.[5–7] One recent study found that ED visits and hospital admissions due to ADRs among seniors in Canada cost an estimated $35.7 million, with more than 80% of those costs arising from hospitalization.[7]

Drugs most commonly associated with ADRs include antibiotics, anticoagulants, antineoplastic drugs, non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics.[2, 6, 8–10] Other factors known to increase the risk of ADRs include a patient's age and sex, the presence of comorbidities, the number of drugs a patient is taking, whether or not a patient has recently started a new drug therapy, the number of pharmacies visited, the number of prescribers used and whether or not a patient had been hospitalized during the previous year.[4–13]

Seniors are at greater risk for ADRs, as well as other types of drug-related adverse events, due to the number of drugs they take, their higher prevalence of certain chronic conditions and age-related changes in the body.[8, 14]

Federal Identity Program

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At the heart of data

Canadian Institute for Health Information
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This analysis uses data from the Discharge Abstract Database (DAD) and the Hospital Morbidity Database (HMDB), both held by the Canadian Institute for Health Information (CIHI), from all Canadian provinces and territories to address questions related to the prevalence of ADR-related hospitalizations in seniors (people age 65 and older), including the types of drugs used and the reactions associated with these hospitalizations.

Linkable drug claims data from the National Prescription Drug Utilization Information System (NPDUIS) Database, also held by CIHI, from seniors on public drug programs in three provinces (Alberta, Manitoba and Prince Edward Island) is used to assess potential risk factors for ADR-related hospitalization. The factors assessed include age, sex, number of concurrent drugs, number of prescribers and number of dispensing pharmacies. Linked drug claims data is also used to compare seniors' drug therapies pre-admission and post-discharge to see how often hospitalization for an ADR leads to changes in drug therapy.

Methods

Discharge Abstract Database and Hospital Morbidity Database

The DAD and HMDB contain demographic, administrative and clinical data on acute care institution separations (discharges, deaths, sign-outs and transfers). Facilities in all provinces and territories except Quebec are required to report data to the DAD. Quebec acute inpatient records are submitted to CIHI through a different process and are included in the HMDB. The HMDB is populated by a subset of DAD data for other jurisdictions. For this analysis, data for stillborn infants, cadaveric donors and discharges from non-acute facilities was excluded.

National Prescription Drug Utilization Information System Database

The drug claims data used in this analysis comes from the NPDUIS Database, as submitted by the public drug programs in Alberta, Manitoba and P.E.I., the three provinces for which linkable data is available. Although not included in this analysis, the NPDUIS Database also contains data submitted by provincial public drug programs in Saskatchewan, Ontario, New Brunswick and Nova Scotia, as well as the federal First Nations and Inuit Health Branch drug program. The NPDUIS Database houses pan-Canadian information related to public program formularies, drug claims, policies and population statistics. It was designed to provide information that supports accurate, timely and comparative analytical and reporting requirements for the establishment of sound pharmaceutical policies and the effective management of Canada's public drug benefit programs.

The NPDUIS Database includes claims accepted by public drug programs, either for reimbursement or toward a deductible,[i] regardless of whether or not the patient actually used the drugs.

The NPDUIS Database does not include information regarding

- Drugs dispensed in hospitals;
- Prescriptions that were written but never dispensed;
- Prescriptions that were dispensed but for which the associated drug costs were not submitted to, or not accepted by, the public drug programs; or
- Diagnoses or conditions for which prescriptions were written.

i. In Saskatchewan and Manitoba, this includes accepted claims for people who are eligible for coverage under a provincial drug program but who have not submitted an application and, therefore, do not have a defined deductible.

Data Linkage

DAD data was linked to NPDUIS Database data for Alberta, Manitoba and P.E.I., the provinces for which CIHI holds linkable NPDUIS Database data. As the NPDUIS Database contains drug claims data from provincial public drug programs, the linked analyses focused solely on seniors, the sub-population for which the most complete drug claims data was available in all three provinces and which is at the highest risk for ADRs. From 2006–2007 to 2010–2011, 15,546 seniors were admitted to hospital for ADRs, as defined in this analysis, in the three provinces studied. For 15,103 (97.2%) of these patients, at least one drug claim was available in the NPDUIS Database during the study period. See Appendix A for a description of the senior populations in these databases.

Definitions

1. **Claimants:** Seniors who had at least one claim accepted by a public drug program, either for reimbursement or toward a deductible.[ii]
2. **External cause code:** A code used to classify an environmental event or circumstance as the cause of injury, poisoning or other adverse effect.
3. **Most responsible diagnosis:** The diagnosis responsible for the greatest portion of the length of stay or greatest use of resources.
4. **Number of drugs:** The number of distinct drugs (as defined by Anatomical Therapeutic Chemical level 5) claimed by a senior during a given year. This does not necessarily reflect the number of drugs he or she took at one time (for example, most non-prescription therapies are not included) and does not include drugs for which claims were not submitted to, or accepted by, the public drug program.
5. **Post-admission comorbidity:** A condition arising following admission that contributed to the length of stay or resource use.
6. **Pre-admission comorbidity:** A condition existing prior to admission that contributed to the length of stay or resource use.
7. **Secondary diagnosis:** A condition existing prior to admission that did not contribute to the length of stay or require resource use beyond maintenance of the condition.

Drug Classification Systems

Two drug classification systems were used in this analysis. In the NPDUIS Database, drugs are identified by drug identification numbers (DINs) assigned by Health Canada and by WHO Anatomical Therapeutic Chemical (ATC) codes.[15] In the DAD, drugs are identified using the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Canada* (ICD-10-CA).[16]

Identifying Adverse Drug Reactions

The WHO defines ADRs as adverse effects of a drug that was properly administered in the correct dose, for therapeutic or prophylactic (that is, preventive) use.[1] This definition excludes both intentional and unintentional poisonings, which are characterized by either an overdose of a prescribed substance or the wrong substance being given or taken in error.

ii. In Saskatchewan and Manitoba, this includes seniors who had accepted claims who were eligible for coverage under a provincial drug program but who had not submitted an application and, therefore, did not have a defined deductible.

The methodology for identifying ADRs was similar to that used in previous studies that have used ICD codes to identify hospitalizations due to ADRs.[2, 5, 7, 10, 13] We identified abstracts that contained

1. A most responsible diagnosis code that was either drug-related or due to a drug (Appendix B),[iii] provided that the most responsible diagnosis was not indicated to have occurred post-admission; or
2. A pre-admission comorbidity[iv] that was either drug-related or due to a drug (Appendix B); or
3. An external cause code that was drug-related (ICD-10 codes Y40 to Y59).

As noted, cases where the most responsible diagnosis occurred post-admission (1.5% of ADR-related hospitalizations) were excluded. These cases were identified when the same diagnosis was coded as both the most responsible diagnosis and a post-admission comorbidity.

When an ADR was identified by an external cause code only, abstracts that also contained a post-admission comorbidity were excluded, as it was not possible to determine whether the drug-related diagnosis occurred pre- or post-admission.[v] Post-admission ADRs were excluded, as it was not known whether they would have required hospital treatment had they occurred outside of the hospital.

Identifying Post-Hospitalization Changes in Therapy

Post-hospitalization changes in drug therapy were identified by comparing patients' drug claims in the 365 days prior to ADR-related admissions with their claims in the 365 days following discharge. Patients without claims in either of the two periods were excluded from the analysis (11.4% of patients who had claims prior to hospitalization did not have claims following hospitalization). Four types of changes were examined: starts, stops, switches and dosage changes.

Patients were considered to have started a drug (as defined by the ATC level 5 code) if they had a claim for that drug in the post-hospitalization period but did not have a claim for that drug in the pre-hospitalization period. Conversely, if patients had a claim for a drug in the pre-hospitalization period but not in the post-hospitalization period, they were considered to have stopped taking that drug.

Switches were identified as cases where patients stopped taking one drug but started taking another drug in the same drug class (for example, anticoagulants). At this level, classes are, in theory, regarded as groups of different drugs that act on the same organ or system in a similar manner to treat similar medical conditions.

Dosage changes were identified as cases where patients stopped taking a particular strength or form of a given drug but started taking another strength or form of the same drug.

Identifying Risk Factors for ADR-Related Hospitalization

Relative ADR risk associated with various factors was measured by performing a logistic regression using drug claims and hospital discharge data for seniors on public drug programs in Alberta, Manitoba and P.E.I. in 2009–2010. In total, 520,308 seniors had drug claims accepted by the public drug programs in these three provinces in 2009–2010.

iii. Codes that included both drug-related diagnoses and other diagnoses were excluded.

iv. This rule was not used in Quebec, as pre-admission comorbidities cannot be distinguished from secondary diagnoses (which do not significantly influence treatment or length of stay) in Quebec data.[17]

v. Including these cases increases the number of ADR-related hospitalizations of seniors as a percentage of total hospitalizations from 2.7% to 4.4% between 2006–2007 and 2010–2011.

Risk factors for (or variables independently associated with) ADRs were identified using hospital discharge and drug claims data from 2009–2010. Drug claims were used to determine the number of unique drugs that seniors claimed and the numbers of prescribers and pharmacies visited in 2009–2010. Discharge abstracts were used to determine whether or not the seniors had been hospitalized, for an ADR or another reason, during that same year. The dependent variable captured whether or not seniors were hospitalized for an ADR in 2010–2011. Overall, 0.6% of seniors on public drug programs in Alberta, Manitoba and P.E.I. in 2009–2010 were hospitalized for an ADR in 2010–2011.

Limitations

Identifying ADRs retrospectively using administrative hospital data is likely to underestimate the prevalence of ADR-related hospitalizations, as necessary data may be missing or inaccurately recorded.[5, 6, 18] Although study design has been shown to affect the estimated prevalence of ADRs, results appear to be similar across studies in terms of the most commonly associated drug classes and other ADR characteristics.[6, 19]

Between 2006–2007 and 2010–2011, 57.0% of hospital discharge abstracts for seniors contained pre-admission comorbidities.[vi] For these cases, it is not possible to determine with certainty whether the external cause code was related to the most responsible diagnosis or one of the pre-admission comorbidities; therefore, it is not possible in most cases to determine which diagnosis was the ADR. It is also not known which diagnosis or diagnoses led to the patient being hospitalized. However, it is known that the patient experienced an ADR prior to admission for which he or she received hospital care.

Although linkage rates were quite high overall (97.2% of patients hospitalized for an ADR had a drug claim in the NPDUIS Database), they dropped when a linkage criterion was added that required a patient to have a claim for the drug identified as being responsible for the ADR on the discharge abstract. For example, even after excluding patients with no linkable NPDUIS Database records, only 84.8% of patients hospitalized with an ADR coded as being related to anticoagulants had a claim for an anticoagulant in the 365 days prior to hospitalization (Table 1). Among the five drug classes[vii] most commonly associated with ADR-related hospitalization, glucocorticoids had the next-highest linkage rate, at 82.4%, while opioids and NSAIDs had rates of 78.1% and 62.6%, respectively, among patients with a related hospitalization. The linkage rate for antineoplastic drugs, which include cancer therapies, was only 10.8%; it is expected that the majority of these drugs would typically be administered in hospitals or ambulatory clinics, which would result in fewer claims appearing in the NPDUIS Database. Other reasons for the lower linkage rates may include the differences in drug classification between the two data sources, drugs being misclassified in discharge abstracts or claims not being submitted to the public drug program (for example, over-the-counter drugs such as some NSAIDs, drugs paid for out of pocket or claims submitted to a private payer). Hospital abstracts were included in this analysis, regardless of whether the patient had a claim for the related drug in the NPDUIS Database prior to the hospitalization.

vi. This calculation excludes abstracts from Quebec, as pre-admission comorbidities cannot be distinguished from secondary diagnoses (which do not significantly influence treatment or length of stay) in Quebec data.[17]

vii. Drug classes were identified in the NPDUIS Database by ATC code, as follows: **anticoagulants:** B01—antithrombotic agents; **antineoplastic drugs:** L01—antineoplastic agents; **opioids:** N02A—opioids; **NSAIDs:** M01A—anti-inflammatory and antirheumatic products, non-steroids; **glucocorticoids:** H02AB—glucocorticoids; R03BA—glucocorticoids; and R03AK—adrenergics and other drugs for obstructive airway diseases.

Table 1: Percentage of ADR-Related Hospitalizations of Seniors With NPDUIS Database Claims for Related Drug, by Days Between Last Claim and Admission, Selected Drug Classes* and Provinces,† 2006–2007 to 2010–2011

Drug Class	≤30 Days	≤365 Days
Anticoagulants	48.9%	84.8%
Antineoplastic Drugs	5.6%	10.8%
Opioids and Related Analgesics	59.7%	78.1%
Glucocorticoids and Synthetic Analogues	51.5%	82.4%
NSAIDs‡ (Excluding Salicylates)	34.9%	62.6%

Notes

* The five drug classes most commonly associated with ADR-related hospitalizations.

† The three provinces submitting linkable data to the DAD and the NPDUIS Database as of July 2012: Alberta, Manitoba and Prince Edward Island.

‡ Non-steroidal anti-inflammatory drugs.

Sources

National Prescription Drug Utilization Information System Database, Discharge Abstract Database and Hospital Morbidity Database, Canadian Institute for Health Information.

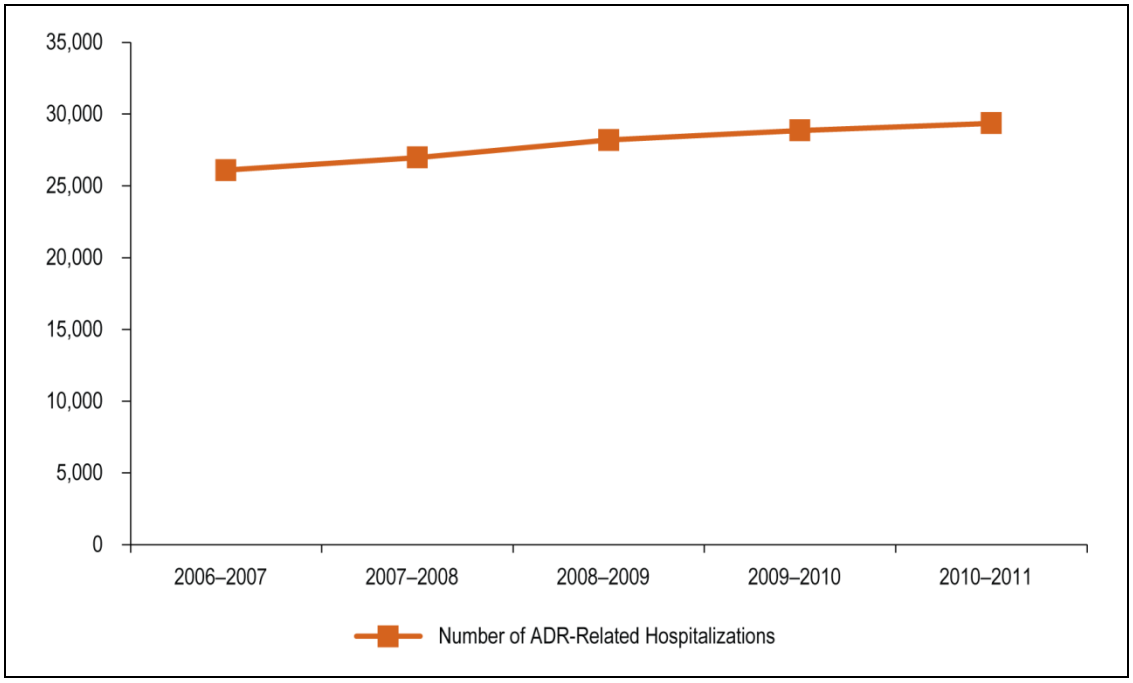
Analysis

The analysis is presented in two sections. The first section contains an analysis of hospital discharge data for all Canadian provinces and territories. This analysis provides an overview of the prevalence of ADR-related hospitalizations, the drugs most frequently related to ADR-related hospitalizations and the most common types of ADRs. The second section contains an analysis of hospital discharge data linked with drug claims data for Alberta, Manitoba and P.E.I. This analysis examines the relationship between various potential risk factors and their association with hospitalization for an ADR. It also compares seniors' drug therapies pre-admission and post-discharge to see how often hospitalization for an ADR led to changes in drug therapy.

How Often Are ADR-Related Hospitalizations Identified in Hospital Discharge Abstracts?

In 2010–2011, 1 in 200 Canadian seniors (more than 27,000 seniors) was identified as having an ADR-related hospitalization. In the same period, 1 in 1,000 Canadian non-seniors was identified as having an ADR-related hospitalization. Between 2006–2007 and 2010–2011, the number of seniors with identified ADR-related hospitalizations (hereafter referred to as ADR-related hospitalizations) increased at an average annual rate of 3.0% (Figure 1). During this period, ADR-related hospitalizations remained relatively stable as a proportion of all hospitalizations among seniors, accounting for between 2.6% and 2.8% in each of the five years. As previously mentioned, ADRs are known to be under-reported in administrative data, so the true rate of ADR-related hospitalizations is likely higher than the rate estimated in this analysis (see the Limitations section for further details).[5, 6, 18]

Figure 1: Number of ADR-Related Hospitalizations Among Seniors, Canada, 2006–2007 to 2010–2011



Sources
Discharge Abstract Database and Hospital Morbidity Database, Canadian Institute for Health Information.

Though seniors represented 14.2% of the Canadian population in 2010–2011, they accounted for 57.6% of the ADR-related hospitalizations that occurred between 2006–2007 and 2010–2011. ADR-related hospitalizations accounted for 2.7% of seniors' hospitalizations between 2006–2007 and 2010–2011, while they accounted for only 1.0% of hospitalizations among non-seniors.

Nearly all ADR-related hospitalizations (97.0%) were identified by the presence of a drug-related external cause code (Table 2). A smaller proportion had a drug-related most responsible diagnosis code (8.1%) or a drug-related pre-admission comorbidity (10.2%).[viii] The proportions were similar when this was restricted to data from Alberta, Manitoba and P.E.I.; the difference in the proportion of ADRs identified by a pre-admission comorbidity (14.9% in the three provinces compared with 10.2% in all provinces and territories) is due to the fact that Quebec does not uniquely identify pre-admission comorbidities in its abstract data.

Table 2: Number of Seniors' ADR-Related Hospitalizations and Percentage of All Seniors' ADR-Related Hospitalizations, by Selection Criteria, 2006–2007 to 2010–2011

Province/Territory	ADR Most Responsible Diagnosis	ADR Pre-Admission Comorbidity	ADR External Cause Codes	Total ADRs
Alta., Man., P.E.I.	1,441 (8.3%)	2,590 (14.9%)	16,873 (96.9%)	17,405
All Provinces and Territories	11,240 (8.1%)	14,251 (10.2%)	135,294 (97.0%)	139,480

Sources
Discharge Abstract Database and Hospital Morbidity Database, Canadian Institute for Health Information.

viii. As well, 15.2% of ADR-related hospitalizations were identified by more than one code (for example, a main diagnosis code and an external cause code).

Which Drugs Are Most Commonly Associated With ADR-Related Hospitalizations?

Anticoagulants were the drug class most commonly associated with ADR-related hospitalizations, accounting for 12.6% of ADR-related hospitalizations between 2006–2007 and 2010–2011 (Table 3). The most common diagnosis associated with anticoagulants was bleeding. Previous studies have found anticoagulants to be among the drug classes most commonly associated with ADRs.[2, 6, 8–10, 20]

Table 3: Top 10 Drug Classes Most Commonly Associated With Seniors' ADR-Related Hospitalizations, 2006–2007 to 2010–2011

Drug Class	Common Uses	Most Common Diagnosis Related to Hospitalization	Percentage of ADRs
Anticoagulants	Heart attack and stroke prevention	Hemorrhagic disorder (bleeding) due to circulating anticoagulants	12.6%
Antineoplastic drugs	Cancer	Neutropenia (low white blood cell count)	12.1%
Opioids and related analgesics	Pain management	Constipation	7.4%
Glucocorticoids and synthetic analogues	Asthma	Chronic obstructive pulmonary disease with acute lower respiratory infection	6.9%
NSAIDs* (excluding salicylates)	Arthritis, pain management, inflammation	Gastric ulcer, chronic or unspecified with hemorrhage (bleeding)	4.9%
Beta-adrenoreceptor antagonists, not elsewhere classified	Heart failure, high blood pressure, angina (chest pain)	Bradycardia (low heart rate), unspecified	4.6%
Other (non-thiazide, low-ceiling) diuretics	Heart failure, high blood pressure	Hypo-osmolality and hyponatremia (low blood sodium)	3.6%
Benzothiadiazine derivatives (thiazide diuretics)	High blood pressure	Hypo-osmolality and hyponatremia (low blood sodium)	3.2%
Cardiac-stimulant glycosides and drugs of similar action (e.g. digoxin)	Heart failure, arrhythmia (irregular heartbeat)	Bradycardia (low heart rate), unspecified	3.1%
Antipsychotics	Symptoms of dementia, schizophrenia, bipolar disorder	Disorientation, unspecified	2.7%

Note

* Non-steroidal anti-inflammatory drugs.

Sources

Discharge Abstract Database and Hospital Morbidity Database, Canadian Institute for Health Information.

A clinical challenge with anticoagulants, particularly vitamin K antagonists such as warfarin, is that they have a narrow therapeutic window and require careful monitoring. Patients vary in how they respond to anticoagulants.[21, 22] Frequent blood testing is required to first determine and then maintain an effective and safe dose.[21, 22] Newer anticoagulants that elicit more consistent patient responses and therefore require less monitoring have been developed, though they have not been shown to significantly lower the risk of bleeding compared with carefully monitored warfarin therapy.[22]

In an effort to minimize the risk of bleeding, different medication management strategies have been put in place, including specialized care clinics and patient self-management.[23–25]

Specialized care clinics schedule and monitor patients' blood tests, determine how much medication patients need, monitor for drug interactions and educate patients about taking their medications appropriately.[24, 25] These clinics have been shown to improve patients' medication management, though not all studies have shown that they reduce the risk of bleeding.[24–26]

In patient self-management, patients are taught to do their own blood tests, communicate the results to their health professionals and manage any dosage changes prescribed to them. Although patient self-management has not been shown to reduce the risk of bleeding, it has been shown to improve patient satisfaction without increasing the risk of bleeding.[24, 25]

Other drugs commonly associated with ADR-related hospitalizations were antineoplastic drugs and opioids and related analgesics. The most common diagnosis associated with ADR-related hospitalizations due to antineoplastic drugs was neutropenia (a low white blood cell count), while the most common diagnosis associated with opioid-related hospitalizations was constipation. Patients receiving chemotherapy may be prescribed colony-stimulating factors to reduce the risk of neutropenia or antibiotics to reduce the risk of infections due to their low white blood cell counts.[27] Risk of constipation can be reduced with dietary changes or treatment with laxatives.[28]

What Are the Most Common Types of ADR-Related Hospitalizations?

The most common ADRs requiring hospitalization were bleeding due to anticoagulants and neutropenia (low white blood cell count) due to antineoplastic drugs (Table 4). Neutropenia is known to be a common side effect of certain types of chemotherapy.[27, 29, 30] Two other diagnoses related to antineoplastic drugs—fever and dehydration—were also among the 10 most common ADRs requiring hospitalization. As mentioned, in cases where multiple pre-admission diagnoses existed, it was not possible to determine with certainty which diagnosis was drug-related.

Table 4: Top 10 Diagnoses and Drug Class Combinations Most Commonly Associated With Seniors' ADR-Related Hospitalizations, 2006–2007 to 2010–2011

Diagnosis Related to Hospitalization	Drug Class	Percentage of ADRs
Hemorrhagic disorder (bleeding) due to circulating anticoagulants	Anticoagulants	6.6%
Neutropenia (low white blood cell count)	Antineoplastic drugs	4.1%
Bradycardia (slow heart rate), unspecified	Beta-adrenoreceptor antagonists, not elsewhere classified	2.1%
Fever, unspecified	Antineoplastic drugs	1.9%
Hypo-osmolality and hyponatremia (low blood sodium)	Benzothiadiazine derivatives (thiazide diuretics)	1.5%
Dehydration	Antineoplastic drugs	1.2%
Constipation	Opioids and related analgesics	1.2%
Chronic obstructive pulmonary disease with acute lower respiratory infection	Glucocorticoids and synthetic analogues	1.1%
Congestive heart failure	Anticoagulants	1.0%
Atrial fibrillation	Anticoagulants	1.0%

Sources
Discharge Abstract Database and Hospital Morbidity Database, Canadian Institute for Health Information.

Which Factors Affect the Likelihood of an ADR-Related Hospitalization?

Linkable drug claims data from the NPDUIS Database from seniors on public drug programs in three provinces (Alberta, Manitoba and P.E.I.) was used to assess potential risk factors for ADR-related hospitalization. From 2006–2007 to 2010–2011, 15,546 seniors in these three provinces were admitted to hospital for ADRs. For 15,103 (97.2%) of these patients, drug claims data was available in the NPDUIS Database. The proportion of patients for whom drug claims could be matched to the drug associated with their hospitalization (for example, whether a patient hospitalized with an ADR related to an anticoagulant had a claim for an anticoagulant) varied between drug classes (see the Limitations section for further details).

New Starts

Studies have shown that the highest risk of an ADR occurs in the days shortly after starting a new drug therapy; however, the timing of ADRs depends on the drug, and some ADRs are more often associated with continued exposure over time.[31–35] ADRs are less likely to occur if patients have been taking a drug for a longer period because they have shown, and may have developed, a tolerance to certain side effects of the drug. Also, if patients have been taking a drug for a longer time period, it is more likely that they have been stabilized on a dose that is appropriate for them. This may reduce the risk of ADRs, as many are dose-related.[35]

To assess the relationship between new starts and ADR-related hospitalizations, ADRs related to two of the most common drug classes—anticoagulants and opioids—were examined. Antineoplastic drugs were not examined due to a lack of linkable drug claims data (see the Limitations section for further details). In this analysis, seniors were defined as starting a new drug therapy if they had a claim for a drug for which they had no claims in the previous 365 days, and they had at least one claim for another drug in those 365 days. ADRs among patients who had no claims for the related drug class in the 365 previous days were excluded (15.2% of anticoagulant-related ADRs and 21.9% of opioid-related ADRs were excluded; see the Limitations section for further details).

Among seniors in Alberta, Manitoba and P.E.I. who were hospitalized for an ADR related to anticoagulants between 2006–2007 and 2010–2011, 8.7% of patients had started an anticoagulant within 30 days of being hospitalized (Table 5), while 28.2% of ADRs associated with anticoagulants occurred within a year of starting therapy. The high proportion (71.8%) of anticoagulant-related hospitalizations that occurred more than a year after starting therapy underscores the importance of ongoing monitoring of anticoagulant therapy.

Among ADRs associated with opioids, 33.2% occurred within 30 days of a patient starting therapy, while 72.4% occurred within a year of starting therapy. The higher proportion of opioid-related hospitalizations that occurred within 30 days of starting therapy is likely related to the fact that patients often develop a tolerance to certain common side effects, such as delirium, disorientation and nausea.[36, 37] In this analysis, delirium and disorientation were found to be the next most common diagnoses associated with opioid-related hospitalizations, after constipation. Constipation can be managed with dietary changes or treatment with laxatives.[28, 36, 37]

Table 5: Percentage of ADR-Related Hospitalizations, by Number of Days Between Hospitalization and New Drug Start and by Drug Class, Selected Provinces,* 2006–2007 to 2010–2011

Days to New Start	Anticoagulants	Opioids
≤5 Days	1.3%	12.6%
≤10 Days	3.5%	20.4%
≤15 Days	5.3%	24.8%
≤30 Days	8.7%	33.2%
≤365 Days	28.2%	72.4%

Note

* The three provinces submitting linkable data to the DAD and the NPDUIS Database as of July 2012: Alberta, Manitoba and Prince Edward Island.

Sources

National Prescription Drug Utilization Information System Database, Discharge Abstract Database and Hospital Morbidity Database, Canadian Institute for Health Information.

To assess the relative risk associated with a patient starting anticoagulant and opioid therapy,[ix] these patients were compared with new users of statins,[x] a class of drugs known to have a relatively low risk of ADRs that would require hospitalization (Table 6). Only 0.11% of new statin users were hospitalized for an ADR within 30 days of starting therapy, which was significantly lower than the risk associated with anticoagulants (0.49%) and opioids (0.43%). It should be noted that, as previously mentioned, the number of ADR-related hospitalizations is likely underestimated in this analysis (see the Limitations section for further details).

Table 6: Percentage of ADR-Related Hospitalizations Among New Drug Starts, by Number of Days Between Hospitalization and New Drug Start and by Drug Class, Selected Provinces,* 2006–2007 to 2010–2011

Days to New Start	Anticoagulants (95% Confidence Interval)	Opioids (95% Confidence Interval)	Statins (95% Confidence Interval)
≤5 Days	0.06% (0.05%–0.08%)	0.11% (0.10%–0.12%)	0.02% (0.01%–0.02%)
≤10 Days	0.18% (0.15%–0.20%)	0.21% (0.20%–0.23%)	0.04% (0.03%–0.05%)
≤15 Days	0.28% (0.25%–0.32%)	0.28% (0.26%–0.30%)	0.06% (0.05%–0.07%)
≤30 Days	0.49% (0.45%–0.53%)	0.43% (0.41%–0.45%)	0.11% (0.09%–0.12%)
≤365 Days	1.89% (1.81%–1.96%)	1.53% (1.49%–1.58%)	0.70% (0.66%–0.74%)

Note

* The three provinces submitting linkable data to the DAD and the NPDUIS Database as of July 2012: Alberta, Manitoba and Prince Edward Island.

Sources

National Prescription Drug Utilization Information System Database, Discharge Abstract Database and Hospital Morbidity Database, Canadian Institute for Health Information.

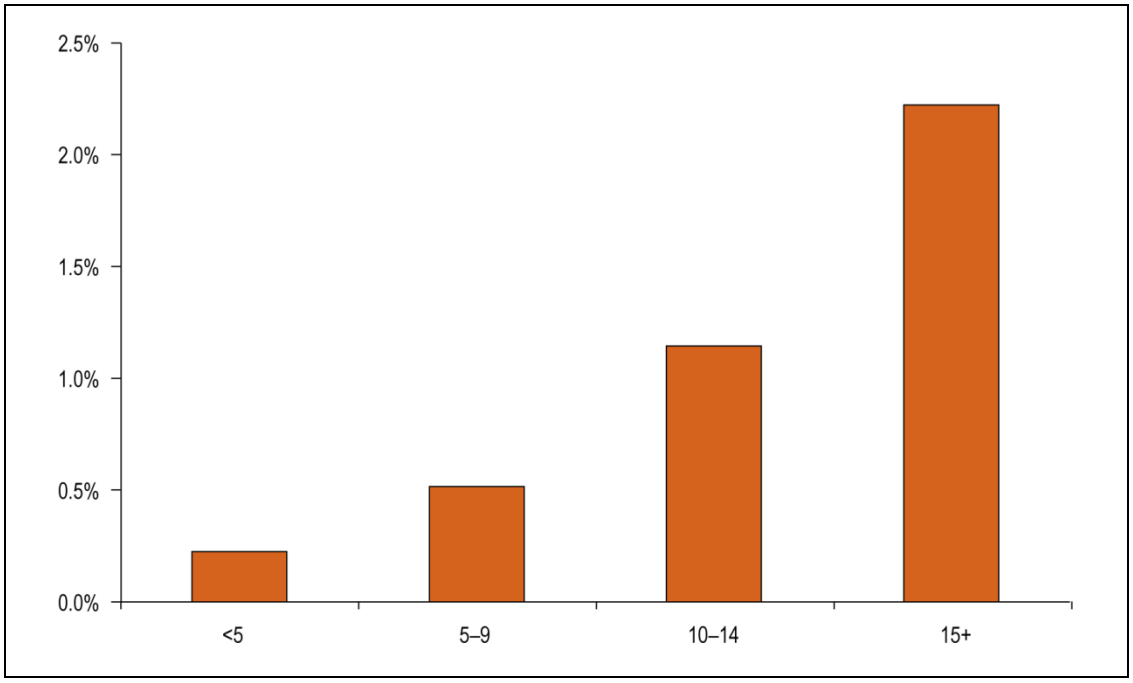
Number of Drugs

As might be expected, seniors who took a higher number of drugs were more likely to be hospitalized for an ADR. Only 0.2% of seniors on public drug programs who had claims for fewer than five drugs in 2009–2010 were hospitalized for an ADR in 2010–2011, while 2.2% of patients who claimed 15 drugs or more were hospitalized (Figure 2).

ix. Anticoagulants and opioids were identified by the ATC codes B01—antithrombotic agents and N02A—opioids, respectively.

x. Statins were identified by the ATC code C10AA—HMG CoA reductase inhibitors.

Figure 2: Percentage of Seniors on Public Drug Programs Hospitalized for an ADR, by Number of Drugs, Selected Provinces,* 2010–2011



Note

* The three provinces submitting linkable data to the DAD and the NPDUIS Database as of July 2012: Alberta, Manitoba and Prince Edward Island.

Sources

National Prescription Drug Utilization Information System Database, Discharge Abstract Database and Hospital Morbidity Database, Canadian Institute for Health Information.

It is sometimes necessary for seniors, particularly those with multiple chronic conditions, to take multiple drugs to manage their conditions. The use of a higher number of drugs is associated with a higher risk of ADRs and other adverse events such as drug interactions.[38–40] Regular reviews of patients' medications by their physicians and pharmacists can help reduce these risks.[41] Medication reconciliation, a process where medications are systematically reviewed at care transition points (for example, when a patient is admitted to hospital) can also help reduce the risk of ADRs by ensuring that any changes in medication that occur at these points are assessed and documented.[42]

The effectiveness of any medication review is limited by the information available to the person conducting it.[43, 44] It is important for patients, where possible, to inform their physicians and pharmacists of all drugs they are taking, including those prescribed by other physicians or obtained over the counter (that is, without a prescription). The implementation of drug information systems, a key component of the electronic health record, has been at least partially completed in several provinces to date.[45] These systems will provide access to more complete information on patients' medications.[45]

Other Factors Associated With ADR-Related Hospitalizations

Relative ADR risk associated with various factors was measured by performing a logistic regression using drug claims and hospital discharge data for seniors on public drug programs in Alberta, Manitoba and P.E.I. in 2009–2010. The potential risk factors examined were consistent with those from previous studies: patient age and sex, the number of drugs a patient was taking, the numbers of pharmacies and prescribers visited, and whether or not a patient had been hospitalized during the previous year.[4–13] The dependent variable captured whether or not seniors were hospitalized for an ADR during 2010–2011.

Older seniors and males were more likely to be hospitalized for ADRs (Table 7). Seniors age 85 and older were 1.7 times more likely to have an ADR-related hospitalization than seniors age 65 to 74, while seniors age 75 to 84 were 1.5 times as likely. This finding is consistent with those of previous studies, which have found that the likelihood of being hospitalized for an ADR increases with age.[4–13] Men were slightly (1.1 times) more likely than women to have an ADR-related hospitalization. Previous studies have found varying results on whether males or females are more likely to experience an ADR.[4–13]

Table 7: Risk Factors for ADR-Related Hospitalizations Among Seniors in Selected Provinces,* 2010–2011

Variable	Value	Odds Ratio (95% Confidence Interval)	p-Value	Percentage of Seniors With Drug Claims in 2009–2010 (n = 520,308)
Sex	Male	1.123 (1.045–1.206)	0.0015	44.0%
	Female	—	—	56.0%
Age Category	65–74	—	—	51.4%
	75–84	1.513 (1.397–1.639)	<0.0001	34.8%
	85+	1.667 (1.509–1.841)	<0.0001	13.7%
Number of Drugs	<5	—	—	38.3%
	5–9	1.978 (1.763–2.219)	<0.0001	39.9%
	10–14	3.752 (3.318–4.243)	<0.0001	15.7%
	15+	6.386 (5.583–7.305)	<0.0001	6.1%
Number of Prescribers	1	—	—	34.0%
	2+	1.300 (1.176–1.437)	<0.0001	66.0%
Number of Pharmacies	1	—	—	69.2%
	2+	0.983 (0.912–1.059)	0.6459	30.8%
Previous Non-ADR Hospitalization	Yes	1.526 (1.408–1.654)	<0.0001	16.3%
	No	—	—	83.7%
Previous ADR Hospitalization	Yes	2.731 (2.262–3.298)	<0.0001	0.6%
	No	—	—	99.4%

Note

* The three provinces submitting linkable data to the DAD and the NPDUIS Database as of July 2012: Alberta, Manitoba and Prince Edward Island.

Sources

National Prescription Drug Utilization Information System Database, Discharge Abstract Database and Hospital Morbidity Database, Canadian Institute for Health Information.

As shown previously in this report, the number of drugs a senior was taking strongly affected the likelihood of that person having an ADR-related hospitalization. Seniors taking 15 or more drugs were 6.4 times more likely than seniors taking fewer than 5 drugs to have been hospitalized for an ADR. Seniors taking 10 to 14 drugs were 3.8 times more likely to have an ADR-related hospitalization, while seniors taking 5 to 9 drugs were 2.0 times as likely. The finding that using a higher number of drugs increases the likelihood of having an ADR is consistent with previous studies.[4–13]

Seniors receiving prescriptions from multiple prescribers were 1.3 times more likely than those with prescriptions from a single prescriber to have been hospitalized for an ADR. With multiple prescribers, it is often more difficult for each one to have a complete picture of a patient's drug regimen. However, it could also be that patients who see multiple prescribers are more at risk due to other factors not controlled for in this analysis (for example, they may, on average, have more severe or a higher number of comorbidities than patients who see only one prescriber). Filling prescriptions at multiple pharmacies did not significantly increase the risk of having an ADR-related hospitalization. Some studies have found that the use of both multiple prescribers and multiple pharmacies can increase the risk of an ADR, while others have not found a significant effect with these factors.[4, 5, 7]

Seniors who were previously hospitalized for something other than an ADR in the previous year were 1.5 times more likely to have been hospitalized for an ADR, while those with a previous ADR-related hospitalization were 2.7 times more likely. This finding is consistent with previous studies.[5, 7]

Some factors noted in the literature could not be examined due to the nature of the data. Previous studies have found that people with more severe or a higher number of comorbidities, those with poor kidney function and people residing in long-term care facilities were all more likely to experience an ADR-related hospitalization or ED visit.[4, 5, 7, 13] One previous study also found that people living in rural areas were more likely to experience an ADR.[13] Alternatively, previous studies have found that patients with a recent ED visit were less likely to have an ADR-related hospitalization, while income level and having a family physician did not significantly affect ADR risk.[4, 5, 7, 13]

Does Hospitalization for an ADR Lead to Changes in Drug Therapy?

To identify changes in drug therapy among seniors hospitalized for ADRs, drug claims in the 365 days prior to admission for ADRs related to anticoagulants and opioids were compared with claims in the 365 days following discharge from hospital. Changes in therapy occurring after ADR-related hospitalizations were then compared with changes following other hospitalizations. Seniors who did not have any drug claims in either the 365 days prior to admission or the 365 days following discharge were excluded.

Between 2006–2007 and 2010–2011, 33.3% of seniors hospitalized for an anticoagulant-related ADR stopped taking at least one anticoagulant following discharge. This is similar to the 36.7% of anticoagulant users with non-ADR-related hospitalizations who stopped using an anticoagulant in the year after discharge. Among those who stopped, only 14.8% of those with anticoagulant-related hospitalizations, and 12.0% of those with non-ADR-related hospitalizations, started taking another anticoagulant.[xi] Anticoagulants are effective in treating often chronic and serious health issues, including reducing the risk of stroke in patients with atrial fibrillation (an irregular heartbeat).[20] It is therefore not surprising that ADR-related hospitalizations did not seem to lead to an increase in stops or switches between anticoagulants.[20]

xi. These numbers were not significantly different from one another at a 95% confidence level. All other numbers compared in this section were significantly different from one another at a 95% confidence level.

Usage patterns differed among those who remained on the same anticoagulants in the year following discharge. Among seniors using the same anticoagulants following discharge, 80.9% of those with anticoagulant-related hospitalizations, compared with only 49.4% of those with non-ADR-related hospitalizations, switched to a new strength or form of the anticoagulants they were taking. The higher number of switches to a new strength or form may be due in part to the narrow therapeutic window of anticoagulants and the variability of patient response.[24]

During the same time period, 68.0% of seniors with opioid-related hospitalizations stopped taking an opioid following discharge, compared with 56.9% of opioid users with non-ADR-related hospitalizations. Among those who stopped, 48.4% of those with opioid-related hospitalizations, compared with only 15.6% of those with non-ADR-related hospitalizations, started taking another opioid in the year following discharge. Patients may switch between opioids if adverse effects prevent them from receiving the dose necessary for adequate pain management.[37]

Among seniors with claims for the same opioids following discharge, 68.0% of those with opioid-related hospitalizations, compared with only 26.1% of those with non-ADR-related hospitalizations, switched to a new strength or form of the opioids they were taking. The higher number of switches to a new strength or form may be due in part to the dosing of opioid therapy. New patients are often started on lower doses to minimize the risk of adverse effects, and the dose is then escalated until a balance between pain relief and manageable adverse effects is achieved.[36, 37] Patients often become more tolerant to certain adverse effects over time, which allows for dose escalation to occur.[36, 37]

Summary

This analysis examined hospital discharge data for seniors in all Canadian provinces and territories from 2006–2007 to 2010–2011 to provide an overview of the prevalence of ADR-related hospitalizations. It also examined the drugs most frequently related to ADR-related hospitalizations and the most common types of ADR-related hospitalizations. Secondary analysis examined hospital discharge data linked with drug claims data for seniors in Alberta, Manitoba and P.E.I. This analysis looked at the relationship between various potential risk factors and the likelihood of being hospitalized for an ADR, and it compared seniors' drug therapy pre-admission and post-discharge to see how often hospitalization for ADRs led to changes in drug therapy.

In 2010–2011, 1 in 200 Canadian seniors (more than 27,000 seniors), compared with 1 in 1,000 non-seniors, was identified as having an ADR-related hospitalization. Between 2006–2007 and 2010–2011, ADR-related hospitalizations remained relatively stable as a proportion of all hospitalizations among seniors, accounting for between 2.6% and 2.8% in each of the five years.

Anticoagulants were the drug class most commonly associated with ADR-related hospitalizations (accounting for 12.6% of ADR-related hospitalizations) between 2006–2007 and 2010–2011. The most common diagnosis associated with hospitalizations due to anticoagulants was bleeding. Several strategies have been used to minimize the risk of anticoagulant-related bleeding, including specialized care clinics and patient self-management.[23–25]

Other drug classes commonly associated with ADR-related hospitalizations included antineoplastic drugs (accounting for 12.1% of ADR-related hospitalizations) and opioids and related analgesics (accounting for 7.4%). Neutropenia (a low white blood cell count) was the diagnosis most commonly associated with antineoplastic drugs, while constipation was most commonly associated with opioids. Patients receiving chemotherapy may be prescribed colony-stimulating factors to reduce the risk of neutropenia or antibiotics to reduce the risk of infections due to their low white blood cell counts.[27] Risk of constipation can be reduced with dietary changes or treatment with laxatives.[28]

Among seniors in Alberta, Manitoba and P.E.I. who were hospitalized for an ADR between 2006–2007 and 2010–2011, ADR-related hospitalizations were more likely among seniors who were older, who were taking a higher number of drugs, who had multiple prescribers and who had been hospitalized in the previous year for any reason. Regular reviews of patients' medications by their physicians and pharmacists can help reduce the risk of ADRs and other adverse events.[41]

Changes in drug therapy (for example, stopping a drug or switching to another drug or dosage) following an ADR-related hospitalization were examined among users of anticoagulants and opioids. Among both anticoagulant and opioid users, dosage changes were much more likely to occur following an ADR-related hospitalization. The higher number of anticoagulant dosage changes may be due in part to their narrow therapeutic window and the variability of patient response.[24] New opioid patients are often started on lower doses to minimize the risk of adverse effects, and the dose is then escalated until a balance between pain relief and manageable adverse effects is achieved.[36, 37]

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Please note that the analyses and conclusions in this document do not necessarily reflect those of the individuals or organizations mentioned above.

Appendix A: Distribution of Total Senior Population, Hospitalized Seniors and Seniors on Public Drug Programs, by Age and Sex, 2010–2011

Canada

Group	Senior Population (n = 4,867,045)	DAD Patients (n = 982,742)
Male	44.4%	46.8%
Female	55.6%	53.2%
65–74	53.4%	41.9%
75–84	33.0%	38.2%
85+	13.5%	19.8%

Alberta, Manitoba and Prince Edward Island

Group	Senior Population (n = 593,915)	DAD Patients (n = 120,436)	NPDUIS Database Claimants (n = 535,808)
Male	44.8%	46.7%	44.4%
Female	55.2%	53.3%	55.6%
65–74	53.0%	41.0%	51.8%
75–84	33.0%	37.6%	34.3%
85+	14.0%	21.4%	13.9%

Sources

Discharge Abstract Database and National Prescription Drug Utilization Information System Database, Canadian Institute for Health Information; Statistics Canada, Demography Division, Special Tabulation, June 2012.

Appendix B: ICD-10-CA Codes Defined as Adverse Drug Reactions

ICD-10-CA Code	Description
D52.1	Drug-induced folate deficiency anaemia
D59.0	Drug-induced autoimmune haemolytic anaemia
D59.2	Drug-induced nonautoimmune haemolytic anaemia
D61.1	Drug-induced aplastic anaemia
D64.2	Secondary sideroblastic anaemia due to drugs and toxins
D68.3	Haemorrhagic disorder due to circulating anticoagulants
D89.3	Immune reconstitution syndrome
E03.2	Hypothyroidism due to medicaments and other exogenous substances
E06.4	Drug-induced thyroiditis
E16.0	Drug-induced hypoglycaemia without coma
E23.1	Drug-induced hypopituitarism
E24.2	Drug-induced Cushing's syndrome
E27.3	Drug-induced adrenocortical insufficiency
E66.1	Drug-induced obesity
G04.0	Acute disseminated encephalitis
G21.0	Malignant neuroleptic syndrome
G21.1	Other drug-induced secondary parkinsonism
G24.0	Drug-induced dystonia
G25.1	Drug-induced tremor
G25.4	Drug-induced chorea
G25.6	Drug-induced tics and other tics of organic origin
G44.4	Drug-induced headache, not elsewhere classified
G61.1	Serum neuropathy
G62.0	Drug-induced polyneuropathy
G72.0	Drug-induced myopathy
H40.6	Glaucoma secondary to drugs
H91.0	Ototoxic hearing loss
I42.7	Cardiomyopathy due to drugs and other external agents
I95.2	Hypotension due to drugs
J70.2	Acute drug-induced interstitial lung disorders
J70.3	Chronic drug-induced interstitial lung disorders
J70.4	Drug-induced interstitial lung disorders, unspecified
K85.3	Drug-induced acute pancreatitis
L10.5	Drug-induced pemphigus
L23.3	Allergic contact dermatitis due to drugs in contact with skin
L24.4	Irritant contact dermatitis due to drugs in contact with skin
L25.1	Unspecified contact dermatitis due to drugs in contact with skin
L27.0	Generalized skin eruption due to drugs and medicaments
L43.2	Lichenoid drug reaction
L56.0	Drug phototoxic response
L56.1	Drug photoallergic response
M10.20	Drug-induced gout, multiple sites
M10.22	Drug-induced gout, upper arm
M10.24	Drug-induced gout, hand

ICD-10-CA Code	Description
M10.25	Drug-induced gout, pelvic region and thigh
M10.26	Drug-induced gout, lower leg
M10.27	Drug-induced gout, ankle and foot
M10.28	Drug-induced gout, other site
M10.29	Drug-induced gout, unspecified site
M32.0	Drug-induced systemic lupus erythematosus
M34.2	Systemic sclerosis induced by drugs and chemicals
M80.40	Drug-induced osteoporosis with pathological fracture, multiple sites
M80.42	Drug-induced osteoporosis with pathological fracture, upper arm
M80.43	Drug-induced osteoporosis with pathological fracture, forearm
M80.45	Drug-induced osteoporosis with pathological fracture, pelvic region and thigh
M80.46	Drug-induced osteoporosis with pathological fracture, lower leg
M80.48	Drug-induced osteoporosis with pathological fracture, other site
M81.4	Drug-induced osteoporosis
M83.5	Other drug-induced osteomalacia in adults
M87.11	Osteonecrosis due to drugs, shoulder region
M87.12	Osteonecrosis due to drugs, upper arm
M87.15	Osteonecrosis due to drugs, pelvic region and thigh
M87.16	Osteonecrosis due to drugs, lower leg
M87.18	Osteonecrosis due to drugs, other site
N14.0	Analgesic nephropathy
N14.1	Nephropathy induced by other drugs, medicaments and biological substances
N14.2	Nephropathy induced by unspecified drug, medicament or biological substance
R50.2	Drug-induced fever
T80.3	ABO incompatibility reaction
T80.4	Rh incompatibility reaction
T80.5	Anaphylactic shock due to serum
T80.6	Other serum reactions
T80.8	Other complications following infusion, transfusion and therapeutic injection
T80.9	Unspecified complication following infusion, transfusion and therapeutic injection
T88.1	Other complications following immunization, not elsewhere classified
T88.2	Shock due to anaesthesia
T88.3	Malignant hyperthermia due to anaesthesia
T88.5	Other complications of anaesthesia
T88.6	Anaphylactic shock due to adverse effect of correct drug or medicament properly administered
T88.7	Unspecified adverse effect of drug or medicament

Source

Canadian Institute for Health Information. *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Canada*. Ottawa, ON: CIHI; 2012.

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